Hospital Topics

Computer prediction of the need for dialysis and transplantation using calculated creatinine clearance

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Abstract

A computerised system capable of prospective assessment of the course of chronic renal failure has been devised. Rapid analysis is possible of the progress of a large cohort of patients and therefore of the prospective load on renal unit facilities. Calculated creatinine clearance values provide a more accurate and earlier prediction of end stage failure than the reciprocals of serum creatinine values.

Introduction

Optimal use of renal dialysis and transplantation facilities can be achieved only if it is possible to assess the progress of disease in chronic renal failure and so determine prospectively the fate of a large cohort of patients.¹

The rate of deterioration in kidney function varies widely even in the same disease.²⁻³ Reciprocal serum creatinine plots have been advocated⁴⁻⁵ but when these are used it is difficult to extrapolate manually from the data in early disease; relative error in laboratory assay is then at its highest,⁶ so that extrapolation of sequential data requires constant reassessment as new data are incorporated. As renal function deteriorates, a fall in creatinine excretion invalidates the simple relation between the reciprocal of serum creatinine and creatinine clearance, and this has contributed to the debate on whether one mathematical function can describe adequately the course of renal disease³ or whether there is accelerated decline as end stage failure approaches.⁷

With a large number of patients it is impractical to attempt accurate, up to date, manual interpretation of data so as to determine the impending load on the facilities of a renal unit. To assess the relative merits of reciprocal serum creatinine and calculated clearance in predicting end stage failure we have developed a computerised system that allows us to obtain reliable forecasts for patients with chronic renal failure and permits assessment of the resulting demand for facilities in any chosen period.

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Methods

Programs were developed on a Hewlett Packard 2000F with Tektronic graphics system and transferred to a Commodore PET with disc storage, high resolution graphics, and a printer for on-line use in the renal unit. Several mathematical functions, including polynomials were used in the program, which was designed to enable prospective assessment of sequential serum creatinine. This was carried out on patients with chronic renal failure attending Manchester Royal Infirmary from 1976 to 1979.

After serum creatinine concentrations had been measured on at least three separate days in each patient, projection of any chosen mathematical function through the data points by a least squares procedure was possible. This enabled us to make a crude initial estimate of when end stage renal failure would occur. Convenient end stage points were chosen as 1.0, 1.5, and 2.0 mmol/l (11.3, 17.0, 22.6 mg/100 ml) (serum creatinine) or 10, 5, and 1 ml/min (creatinine clearance). As each sequential serum creatinine concentration was incorporated, successive further estimates of dates for end stage failure were obtained (fig 1). The process was repeated as disease progressed. Each patient was followed up until haemodialysis or transplantation was undertaken. The validity of the chosen mathe-

FIG 1—Successive estimations of end stage renal failure by least squares best fit of data to linear projections of calculated creatinine clearance.

TABLE 1—Details given by computer printout for case 21: successive estimations of dates for reaching clearances of 10, 5, and 1 ml/min. From data point 7 (24 March 1975), an established disease course was present

No of observations	Date of observations	Estimated dates for clearance at:		
		10 ml/min	5 ml/min	1 ml/min
2	1 April 74	9 April 81	21 Jan 82	7 Sept 82
3	2 April 74	15 Jan 79	28 July 79	2 Jan 80
4	22 April 74	18 Aug 79	25 March 80	18 Sept 80
5	12 Aug 74	7 Oct 75	7 Dec 75	25 Jan 76
6	2 Dec 74	3 Oct 75	3 Dec 75	21 Jan 76
7	24 March 75	9 Dec 75	17 Feb 76	11 April 76
8	14 April 75	14 Dec 75	22 Feb 76	17 April 76
9	14 June 75	11 Dec 75	19 Feb 76	14 April 76
10	7 July 75	12 Dec 75	21 Feb 76	15 April 76
11	1 Sept 75	14 Dec 75	22 Feb 76	17 April 76
12	10 Nov 75	13 Dec 75	21 Feb 76	16 April 76
13	21 Nov 75	7 Dec 75	15 Feb 76	9 April 76
14	3 Dec 75	8 Dec 75	15 Feb 76	9 April 76
15	29 Dec 75	13 Dec 75	21 Feb 76	16 April 76
16	20 Jan 76	15 Dec 75	24 Feb 76	19 April 76
17	9 Feb 76	16 Dec 75	24 Feb 76	19 April 76
18	17 Feb 76	14 Dec 75	22 Feb 76	17 April 76
19	19 Feb 76	13 Dec 75	21 Feb 76	16 April 76
20	20 Feb 76	13 Dec 75	21 Feb 76	16 April 76
21	23 Feb 76	14 Dec 75	22 Feb 76	17 April 76

TABLE II—Twenty five cases of chronic renal failure treated with dialysis at mean clearance 1.8 ml/min; from serum creatinine 0.6 mmol/l (6.8 mg/100 ml) 95% had reached end stage by one year. Comparison of reciprocal of serum creatinine and linear decline in calculated creatinine clearance as predictors of end stage renal failure

Case No	Age at presentation (years)	Renal disease	Presenting clearance (ml/min)	Duration of disease (months)	Average rate of decline of renal function (ml/min/month)	Time (months) before end stage when end stage was predicted		Difference (b) - (a) (months)
						1/Serum creatinine (a)	Calculated creatinine clearance (b)	
1	53	Polycystic kidneys	12	10	1.2	1	6	+5
2	39	Chronic glomerulonephritis	35	48	0.7	7	19	+12
3	43	Diabetic nephropathy	12	13	0.9	5	6	+1
4	20	Mesangial proliferative glomerulonephritis	52	30	1.7	14	14	0
5	33	Bilateral small kidneys	18	39	0.5	1	1	0
6	19	Chronic pyelonephritis	10	12	0.9	6	6	0
7	37	Accelerated hypertension	10	30	0.3	1	1	0
8	43	Accelerated hypertension	12	12	1.0	1	1	0
9	40	Chronic pyelonephritis	10	6	1.4	2	2	0
10	30	Hydronephrosis	10	15	0.6	4	6	+2
11	34	Chronic glomerulonephritis	8	13	0.6	1	2	+1
12	34	Chronic glomerulonephritis	45	36	1.25	4	6	+2
13	30	Bilateral small kidneys	10	11	0.95	1	5	+4
14	15	Focal glomerulonephritis	8	24	0.33	3	3	0
15	40	Focal glomerulonephritis	35	21	1.7	8	6	-2
16	21	Followed ATN postpartum	35	60	0.55	42	42	0
17	19	Chronic pyelonephritis	6	6	1.0	0	0	0
18	27	Interstitial nephritis	18	35	0.5	2	2	0
19	35	Chronic pyelonephritis	9	10	0.9	6	8	+2
20	33	Polycystic kidneys	60	44	1.5	24	24	0
21	26	Proliferative glomerulonephritis	60	25	2.4	9	12	+3
22	38	Membranous glomerulonephritis	90	36	2.5	8	8	0
23	13	Chronic pyelonephritis	7	31	0.22	10	10	0
24	38	Polycystic kidneys	7	10	3.0	4	4	0
25	27	Systemic vasculitis	100	33	0.7	3	6	+3

ATN = Acute tubular necrosis.

TABLE III—Thirty patients with chronic renal failure who underwent transplantation at a mean terminal clearance of 4.6 ml/min. Transplantation preceded predicted end stage of creatinine clearance 1 ml/min in most cases

Case No	Age at presentation (years)	Renal disease	Presenting clearance (ml/min)	Duration of disease course observed (months)	Average rate of decline in renal function (ml/min/month)	Anticipation of predicted end stage creatinine clearance 1 ml/min
26	45	Focal glomerulonephritis	17	120	0.1	72
27	29	Dysplastic kidneys	4.1	19	Nil	0
28	29	Chronic pyelonephritis	6.6	6	Nil	0
29	22	Congenital hypoplastic kidneys	7.1	23	0.1	20
30	53	Unilateral non-functioning kidneys	11	22	0.2	25
31	45	Membranous glomerulonephritis	50	130	0.35	70*
32	37	Chronic pyelonephritis	10	37	0.16	28
33	26	Chronic glomerulonephritis	11	22	0.27	10
34	22	Chronic pyelonephritis	8	20	0.5	9
35	54	Mesangiocapillary glomerulonephritis	34	44	0.72	23
36	17	Hypoplastic kidneys	3.7	70	0.1	27
37	29	Chronic glomerulonephritis	11	14	2.1	12
38	55	Polycystic kidneys	10	14	0.25	19
39	30	Mesangiocapillary glomerulonephritis	73	48	1.3	6
40	47	Analgesic nephropathy	4	9	0.8	7
41	51	Chronic pyelonephritis	10	74	0.1	35
42	54	Chronic pyelonephritis	5	13	Nil	0
43	57	Analgesic nephropathy	4	77	0.03	24
44	26	Polycystic kidneys	2	5	Nil	0
45	50	Chronic glomerulonephritis	11	28	Nil	0
46	28	Chronic pyelonephritis	3	5	Nil	0
47	25	Chronic glomerulonephritis	12	12	0.9	8
48	29	Chronic pyelonephritis	10	58	Nil	0
49	22	Focal sclerosing glomerulonephritis	34	32	0.9	15
50	30	Chronic pyelonephritis	7	17	0.1	50
51	48	Chronic glomerulonephritis	4	21	Nil	0
52	43	Chronic pyelonephritis	15	72	0.15	40
53	22	Mesangiocapillary glomerulonephritis	43	37	1	25
54	29	Chronic glomerulonephritis	18	20	0.5	12
55	55	Chronic pyelonephritis	9	24	0.2	9

*Data clearly fitted logarithmic function.

matial function was assessed on the basis that, as more data were incorporated, successive estimates should give a sequence of end stage predictions that oscillated about a mean value and that the magnitude of the oscillations should diminish as random errors tended to cancel out (table I). Successive estimates erring in one direction would imply that the chosen function did not fit the data.

Results and data interpretation

We examined the data from 55 patients with chronic renal failure. Their creatinine clearances at presentation ranged from 2 to 100 ml/min. Patients had had more than six serum creatinine measurements and had been followed up for over four months. Only two mathematical functions consistently described the relation between serum creatinine and time: (a) a rectangular hyperbola, implying a linear relation between a simple reciprocal of serum creatinine and

time; and (b) a hyperbola modified to compensate for reduction in daily excretion of creatinine as the disease progressed and net retention where serum concentrations were rising substantially.^{8,9} This function also allowed estimation of a calculated creatinine clearance when age, weight, and sex are known.¹⁰ Figure 2 shows the graphical display provided by these two functions for one case.

We observed the progress of each case of chronic renal failure; if three or more successive estimates of end stage, made over at least three months, gave oscillations of not more than three months an "established course of the disease" could be defined (table I, from observation 7). Once the course of the disease was so defined and end stage renal failure reached a retrospective comparison between the estimated and actual end stages allowed us to calculate the earliest time at which end stage could be expected reliably. This was carried out for both simple reciprocal of serum creatinine and calculated creatinine clearance in the 25 patients who reached end stage and were treated with haemodialysis (table II). As a means of predicting end stage a linear decline in calculated creatinine clearance was superior

FIG 2—Comparison of calculated creatinine clearance and reciprocal of serum creatinine (in case 12); the former showed less variance.

Conversion: SI to traditional units—Creatinine: 1 mmol/l $\approx$ 11.3 mg/100ml.

to the reciprocal of serum creatinine in 10 out of 25 cases and inferior in one: mean improvement was 1.4 months. This improvement was significant (paired *t* test, $t=2.50$, $p<0.05$).

All 55 cases were analysed using the linear decline of calculated creatinine; 14 had a presenting clearance of greater than 20 ml/min, and in 13 an established course of the disease was shown; in one (case 31) the data clearly fitted a logarithmic function. In this group nine were treated with dialysis at a mean end stage clearance of 1.3 ml/min, this having been correctly predicted by a mean of 15.2 ± 3.9 (SE) months; in four a calculated creatinine clearance of 1 ml/min was predicted a mean of 17.3 ± 4.3 months ahead, and transplantation was carried out before the predicted end stage at a mean creatinine clearance of 6.5 ml/min (table III).

In 41 cases the clearance at presentation was less than 20 ml/min; an established course of the disease was shown in 32. Of these, 15 were treated with dialysis at a mean end stage clearance of 1.9 ml/min, which was correctly predicted by a mean of 4.2 ± 0.7 months (table II). Seventeen were given transplants (table III): the anticipation of

FIG 3—Assessment of 45 patients with different renal diseases who developed an established course of the disease: course of the disease as assessed by calculated creatinine clearance divided into initial, middle, and terminal thirds and number of patients shown to develop an established course of the disease in each third.

predicted creatinine clearance 1 ml/min was a mean of 23.9 ± 4.2 months. Transplantation was at a mean creatinine clearance of 3.9 ml/min.

Seven cases with presenting clearances less than 11 ml/min showed no net deterioration but were given transplants because of advanced renal failure. One patient (case 17) presented with advanced renal failure with deteriorating function, but an established course of the disease was not defined before end stage was reached. In two cases end stage failure was reached much earlier than expected because of a new disease affecting the kidney; one had superimposed disseminated intravascular coagulation (case 18) and the other a ruptured kidney cyst (case 44). Thirteen out of 14 patients with presenting clearances of greater than 20 ml/min and 32 out of 41 with presenting clearances of less than 20 ml/min were shown to develop an established course of the disease: this was not a significant difference ($\chi^2=1.5$, $p>0.1$). An established disease course was therefore found in patients presenting with both early and advanced renal disease. The type of renal disease did not affect the linearity of decline in renal function (fig 3).

Planning dialysis and transplantation

A further program designed to analyse the data files of patients with chronic renal failure enabled patient lists for management purposes

FIG 4—Assessment of load on renal unit facilities from patients with chronic renal failure for the first quarter of 1982 (patients 3, 4, and 5; for clarity, assessment of five patients only is shown).

to be constructed. Criteria for inclusion may be altered according to requirements—for instance, transplantation is appropriate in those with an established disease course and predicted to reach clearances between 10 and 5 ml/min in 12 to 18 months time¹; patients requiring assessment for dialysis are those reaching clearances of less than 2 ml/min in six months (fig 4). The total load on unit facilities from patients with chronic renal failure in any part or full year in the future may be similarly estimated. This approach to assessing and planning the load of a renal unit is fundamentally different from patient assessment on the basis of current clearance only, since the factor of widely varying rates of decline in renal function (tables II and III) is taken into account.

Discussion

Linear extrapolation of calculated creatinine clearance is a more useful and often more accurate method of monitoring and predicting kidney function in chronic renal failure than is the reciprocal of serum creatinine. Calculations and predictions of end stage are rapid and practical, and the graphic display provided by a computer facilitates interpretation. The benefit of calculated creatinine clearance is greater at low clearances, since errors implicit in reciprocal of serum creatinine due to the accompanying fall in creatinine excretion are then at their highest; this method obviates the necessity for frequent 24 hour urine collections to obtain a measured creatinine clearance.

The concept of an established course of the disease, as defined in this study, is important. It provides an objective assessment

of each patient's disease and shows whether or not there is progression of disease. It forms a basis on which the future load on renal unit facilities may be estimated: end stage estimates for each patient are considered only when a meaningful course of the disease is established. Deviation from an established course of the disease may be observed graphically or be displayed as the sequence of predicted dates: a statistical probability of its occurrence is best assessed by operational research techniques,¹¹ and this would be a valuable incorporation into the present computer system. Such an event occurred in two cases (18 and 44) in this series of 55 patients. Change in the established course of the disease may be brought about by an arrest of the pathological process affecting the kidney and is a basis for assessing the effect of treatment. An observed accelerated decline at any stage is more likely to be real with calculated creatinine clearance than with the reciprocal of serum creatinine, since with the reciprocal net retention of creatinine terminally will exaggerate this trend. Deviation from an established course of the disease should alert the observer to search for a remedial cause: we have shown this after inappropriate use of 1α -hydroxycholecalciferol.¹²

The most reliable predictions of end stage renal failure are in those presenting early in the course of their disease: minor deviations from linearity in the terminal stages assume less relative importance if the whole course of the disease can be studied. Monitoring of patients presenting with both early and advanced renal disease is valuable, and late presentation should not preclude attempted assessment of the course of their disease. As the course of each disease progresses, end stage predictions become more accurate: assessment of demand for support facilities is more accurate for the near future than for the distant,

and assimilation of new patient data enables this to be prospectively and continuously reassessed.

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(Accepted 31 January 1983)

I have been told, in connection with the housekeeping arrangements for an old people's home, that dried milk is preferable to fresh on the grounds of its lower fat content, its added vitamins, and its lower cost. Is this correct?

It is true that dried milk powders can, when reconstituted, provide liquid milk at a marginally lower cost. The generalisations regarding fat content and added vitamins apply to specific products. Only powders prepared from skimmed milk have a proportionately lower fat content and the addition of vitamins to milk powders is by no means the rule.—D A T SOUTHGATE, head, nutrition and food quality division, Food Research Institute, Norwich.

Why does dapsone improve dermatitis herpetiformis?

Few drugs act as quickly and as reliably as dapsone or 4:4 diamino-diphenyl sulphone in dermatitis herpetiformis. The response is such that it remains one of the most important clinical features on which diagnosis is based.¹ Despite this we do not know how it works, and this may not be unrelated to the fact that we do not know how the rash of dermatitis herpetiformis is produced. The drug was found to work for dermatitis herpetiformis in Portugal in 1950 "by accident." There is no doubt that it has antimicrobial properties as its use in leprosy and malaria indicate, but dermatitis herpetiformis does not result from infection and is not helped by other antibacterial agents, with the exception of the sulphonamides. Dapsone is normally given by mouth but works when given intravenously, though not, it seems, when applied topically to the lesions. Few clues about its action come from its use in other conditions, for they have little in common (other blistering diseases, psoriasis, vasculitis, lupus erythematosus, acne, eczema, Crohn's disease, and rheumatoid arthritis). Moreover, these diseases differ from dermatitis herpetiformis in that dapsone acts less quickly and only in a few patients. Under certain experimental conditions dapsone can suppress the Arthus reaction, suppress cell mediated immunity, interfere with immune complex deposition, stop enzyme release from lysosomes, and inhibit complement activation by the alternative pathway. There are, however, objections to all the theories of action in dermatitis herpetiformis based on these observations. Two important aspects of this disease,

the IgA deposits in the skin and the associated gluten sensitive enteropathy are not altered by dapsone but the characteristic worsening of the rash by iodides does not occur if the patient is taking dapsone.

Dapsone is a strong oxidising agent and its main haematological side effects are due to this. The drug's oxidant properties also affect the myeloperoxidase system of polymorphonuclear leucocytes, inhibiting the reaction between it, hydrogen peroxide, and halides.² This theory of the site of action of dapsone would fit with the opposing effects of iodide and dapsone in dermatitis herpetiformis. Polymorphonuclear leucocytes seem to be important for they are the prominent cells seen in the very early papillary tip microabscesses of dermatitis herpetiformis. In short we still do not know why it works.—JANET MARKS, senior lecturer in dermatology, Newcastle upon Tyne.

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What is the effect of phytic acid on calcium absorption?

It is generally believed that phytic acid reduces calcium absorption and when phytic acid intake is high and the calcium intake borderline this can lead to osteomalacia. In Britain this may occur in poorly integrated Indian and Pakistani immigrants consuming large quantities of unleavened bread or chapatis. This diet is thought to be the major contributory factor in the development of rickets and osteomalacia in the British Asian community. The precise mode of action of phytic acid and other constituents in bran on calcium metabolism is not clear, for although these vegetable residues may bind calcium in the lumen of the gut, thus making it unavailable for absorption,¹ it has been suggested² that dietary fibre could extract sufficient amounts of vitamin D metabolites of non-dietary origin from their enterohepatic recirculatory pathway³ to cause an excessive loss of vitamin D in the faeces.—MARK AITKEN, consultant physician, Colchester.

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