Doubling of serum creatinine: is it sensitive and relevant?

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Introduction

The assessment of progression in chronic renal diseases is important to monitor the development of renal insufficiency in individuals, to evaluate the importance of putative progression promoters in observational studies, and to evaluate the effectiveness of treatment on progression in clinical trials. The rate of progression in renal function has been considered a primary end point in clinical trials like time to development of end stage renal disease or death. Usually progression is evaluated by repeated measurements of markers of renal function. The progression can be assessed as the rate of change in the marker, or as the time to an endpoint such as a certain degree of impairment in renal function [1]. The time to doubling of baseline serum creatinine is such an example, which have been applied in several recent large, completed or ongoing, clinical trials evaluating the effect of different treatment modalities on the progression of chronic renal diseases [2–4]. As several studies have suggested serum creatinine to be a poor marker of renal function [5], it seems appropriate to consider the sensitivity and relevance of doubling of serum creatinine as a trial endpoint.

Serum creatinine as a marker of renal function

The renal clearance of inulin during constant infusion has been considered the gold standard for determination of glomerular filtration rate (GFR), but the cumbersome procedures, difficulties with measuring inulin and limited availability has encouraged the search for alternatives. The radioisotope-labelled markers [125I]-lothalamate, [99mTc]-DTPA and [51Cr]-EDTA have been found to give accurate and precise estimates of GFR [1], whether using renal or plasma clearance techniques [6]. The latter method avoids problems with incomplete urine collections, a frequent phenomenon in diabetic patients due to cystopathy. In clinical practice however, measurement of serum creatinine is the most widely used marker of renal function, which can be assessed at a low cost and with little inconvenience for the patient.

There are however several problems related to the use of serum creatinine as a marker of renal function as reviewed by Levey [7]. Firstly there are technical difficulties with interfering substances (glucose, ketones) which can be solved by the use of a reaction kinetic principle. Secondly the level of serum creatinine is not only dependent on the GFR: creatinine does not behave like an ideal filtration marker, there is tubular secretion, which changes with variation in GFR [5], rate of change in the marker, or as the time to an endpoint such as a certain degree of impairment in renal function [1]. The time to doubling of baseline serum creatinine is such an example, which have been applied in several recent large, completed or ongoing, clinical trials evaluating the effect of different treatment modalities on the progression of chronic renal diseases [2–4]. As several studies have suggested serum creatinine to be a poor marker of renal function [5], it seems appropriate to consider the sensitivity and relevance of doubling of serum creatinine as a trial endpoint.

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The Modification of Diet in Renal Disease study [8] concluded that while a significant beneficial effect of low protein diet could not be demonstrated when using a true marker of GFR, such an effect would erroneously have been found if creatinine data had been used [9].

**Doubling of serum creatinine for the assessment of progression**

Despite the above mentioned limitations of serum creatinine as a marker of renal function it has been used in numerous studies, either using the slope of 1/serum creatinine, measured or estimated creatinine clearance, or as time to doubling of serum creatinine. The slope methods gives an absolute rate of loss of renal function per time and is based on the assumption of a linear decline in renal function. Using time to doubling of serum creatinine, it is not necessary to assume the decline to be linear. Although this assumption of linearity is often made and several studies support this, it has not been proven to be the case in all kidney diseases. In contrast using time to doubling of serum creatinine gives a relative expression of progression. If the decline is linear, then the time to doubling of serum creatinine will become less with decreasing GFR, thus it is necessary with similar baseline levels of creatinine to make a comparison of time to doubling of serum creatinine between groups.

From a statistical point of view there are several advantages of using time to doubling of serum creatinine instead of the slope of GFR with time, apart from avoiding the assumption of linearity. It takes several measurements over a period of time, preferably several years, to establish the slope in GFR. Patients dropping out of a study after shorter periods of follow up are thus not eligible for evaluation, in contrast all patients with at least two measurements of serum creatinine are eligible in an analysis of time to doubling of serum creatinine.

When using time to event, such as doubling of serum creatinine, as an endpoint, the methods used to analyse survival data can be applied. This allows the presentation of results using easily understandable survival curves. Confounding variables can be controlled for by using for example Cox regression analysis, which also takes care of drop outs by censoring. Confounders and drop-outs can also be controlled for when applying slope analysis models, although it requires less simple methods [8].

However, in many studies only a small fraction of the patients reaches the endpoint, i.e. doubling of creatinine. These may be ‘fast trackers’, a subgroup with fast progression, having an increased risk of being confounded with different renal diseases. It is also possible that the effect of intervention is different in ‘fast trackers’ compared to ‘slow trackers’. The dichotomous endpoint ‘doubling of serum creatinine’ will not evaluate potential changes within the group of ‘slow trackers’, unless they are followed until reaching the endpoint. It has been suggested that at least 70% of the patients have to reach the endpoint in order to allow proper evaluation [10].

Is it then relevant to use doubling of serum creatinine as an endpoint in clinical trials? As previously discussed this endpoint is not very sensitive, but rather specific if it is demonstrated that the applied intervention is not interfering with the analysis of creatinine (i.e. cephalosporins) or affecting the serum creatinine levels by interference with metabolism and renal handling of creatinine (i.e. low protein diet, and medication such as cimetidine). Furthermore the groups to be compared should be well matched not only regarding the level of serum creatinine but also factors determining the renal creatinine pool. In two patients with differing creatinine pools (determined mainly by gender, age and weight) a doubling from the same baseline creatinine level, corresponds to different changes in GFR. Furthermore it can only be considered relevant, if a reasonable fraction of the patients reach the endpoint within the follow up period. Otherwise there is a large probability of a type 2 error, a false negative outcome. This problem was illustrated by the study of the effect of angiotensin converting enzyme inhibition on diabetic nephropathy by the collaborative study group [3]. The study included 409 patients with diabetic nephropathy. The patients were followed for a median of 3 years (range 1.8–4.8), and were randomized to either captopril or placebo in addition to the usual antihypertensive medication. Sixteen per cent of the patients progressed to the end point, i.e. doubling of baseline serum creatinine. A significant reduction in the risk of doubling of baseline serum creatinine was found overall, but in a subgroup analysis this was not significant in 307 patients with normal serum creatinine at baseline (<1.5 mg/dl). It is possible that angiotensin converting enzyme inhibition has a specific renoprotective effect, beyond lowering of blood pressure, only at certain stages in the development of diabetic kidney disease, i.e. microalbuminuria and severely impaired renal function. It is also very likely, however, that in the groups with normal serum creatinine levels the number of events were too small, making it impossible to detect any potential differences between the groups. A pre-study power calculation should be carried out taking the level of renal function and the expected progression rate into consideration.

**Conclusion**

The use of time to doubling of serum creatinine as an endpoint in intervention trials aiming at reducing the rate of progression in chronic renal disease is cheap, and convenient both for the patient and in the statistical analysis. The specificity is high, when a confounding effect of the intervention can be excluded, and when other factors such as changes in protein intake, muscle mass and concomitant medication, are taken into consideration. Unfortunately the sensitivity is low, particularly in patients with normal renal func-
tion, and the endpoint is only relevant when a sufficient number of events can be expected, i.e. in studies of advanced and fast progressing chronic renal disease. Unless these considerations and limitations can be accounted for, repeated measurements of GFR is recommended in the study of progressive renal disease.

References

The medical and economical advantages of early referral of chronic renal failure patients to renal specialists

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Introduction

Substantial progress has been made in the management of end stage renal disease (ESRD). Nevertheless, the adjusted average annual mortality rate (24%) of dialysis patients in the US remains substantially high [1,2].

Several factors may account for this high mortality including the presence of multiple comorbid conditions (e.g. cardiovascular disease, diabetes, old age), and the clinical status of patients at initiation of renal replacement therapy (RRT). Recently, delayed referral of chronic renal failure (CRF) patients to renal specialists has been described as a factor in the prevalence of comorbid conditions and the increased morbidity and early mortality of ESRD patients commencing RRT [3–8]. Preliminary analysis from wave 2 of the Dialysis Morbidity and Mortality Study (DMMS) in the US showed that only 39% of patients treated with haemodialysis were seen by a nephrologist 3 or fewer months prior to starting dialysis, and 25% were evaluated less than 1 month before they approached ESRD. These percentages were slightly lower among peritoneal dialysis patients [3].

Although clinicians and researchers have long recognized that a variety of early interventions may retard the progression of CRF, the potential value of early referral of CRF patients to renal specialists in terms of impacting on the patient’s co-morbidity is apparently less widely known. In some cases this may represent rationing of increasingly scarce medical resources [4]. In most cases however, it may simply reflect lack of awareness among traditional referral resources.

Late referral (LR), defined as referral to the nephrologist less than 1–6 months prior to the need of RRT, is a common phenomenon seen in ~30–50% of ESRD patients who present to the nephrologist [9] and does not seem to be limited to the US. Studies from France show that 40% of patients are initiated late (creatinine clearance 0–5 ml/min). In the UK the percentage of late initiation due to LR is even higher (95%) [5,6,9]. Thus, LR represents a preventable factor that has received very little attention in the last decade, despite the fact that it has important medical and economical implications for the ESRD population.