A dramatic reduction of normalized protein catabolic rate occurs late in the course of progressive renal insufficiency

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Abstract

Background. Spontaneous reduction in dietary protein intake is a recognized feature of severe renal failure, and previous studies have suggested that this may occur at an early stage of renal functional decline.

Methods. We examined the effects of progressive renal insufficiency on the normalized protein catabolic rate (nPCR) in 1282 patients (mean age 55.8±15.5 years; 60.4% male) over a 7 year period. All values of nPCR (n=5082) obtained before commencement of dialysis were included. A total of 361 (28.2%) patients later developed end-stage renal failure and were started on dialysis.

Results. Cross-sectional analysis showed nPCR being significantly less at lower creatinine clearance. Mean nPCR was 1.17±0.31 at a clearance >50, 1.04±0.27 at 25–50, 0.93±0.21 at 10–25 and 0.74±0.18 at <10 ml/min. Mean nPCR in each clearance group was different from that in all other groups (P<0.001 in all cases). When nPCR was studied longitudinally in relation to time of initiation of dialysis, the fall in nPCR only became significant in the 3 months preceding initiation. Curve fitting suggested a two-phase exponential association between nPCR and renal function, a gentle decline of nPCR in mild and moderate renal failure culminating in a dramatic decline when CrCl reached 15 ml/min and weekly Kt/Vurea 2.5. nPCR at dialysis initiation predicted survival on dialysis even when corrected for age, diabetes and non-renal co-morbid load. However, it was no longer significant when residual renal function was included in the model. The group initiating dialysis with a normal nPCR maintained this throughout the first 3 years on dialysis whilst the group initiating with a low nPCR, though improving initially, continued to have significantly lower nPCR levels throughout follow-up than their normal nPCR counterparts.

Conclusion. A significant reduction of nPCR occurs late in progressive renal insufficiency and may predict the need for dialysis initiation. nPCR levels <0.8 at initiation predict future low nPCR levels and mortality on dialysis. The correlation between nPCR and CrCl in early renal insufficiency may be partly artefactual.

Keywords: chronic renal failure; dialysis; nPCR; nutrition; protein intake; survival

Introduction

Spontaneous reduction in dietary protein intake is a recognized feature of severe chronic renal failure (CRF) [1,2] and is prevalent in dialysis populations [3–6]. There is some evidence that reduction in protein intake starts at an early stage of renal functional decline [7]. Malnutrition is a predictor of morbidity [8,9] and mortality [5,9,10]. Prevention of malnutrition is therefore a central theme in guidelines (DOQI and others) for initiation of dialysis [11,12].

Assessment of nutritional status is fraught with difficulties [13]. Previously accepted markers such as serum albumin are now known to be highly influenced by inflammation [14]. Normalized protein catabolic rate (nPCR) has been widely used as a marker of protein intake [3,15,16]. The protein equivalent of total nitrogen appearance (nPNA), which is similar to nPCR but also takes into account urinary protein losses, is also used. Whilst both these measures are widely used, their inherent assumptions are often not realized. These include (i) non-anabolic/non-catabolic state; (ii) normal liver function; and (iii) stable blood urea.

We studied changes in nPCR in relation to indices of renal function in a large number of pre-dialysis patients with progressive CRF. In the subgroup of patients who subsequently initiated dialysis, we studied the relationship between nPCR at the time of dialysis...
initiation and subsequent outcome on dialysis. The purpose of these studies was to attempt to define the usefulness of this marker of protein nutrition as an aid in deciding the optimum timing of dialysis initiation.

Subjects and methods

Nephrology patients

Patients with renal impairment attend our pre-dialysis clinics with a frequency determined by clinical need. At each clinic visit, in addition to clinical assessment, a number of routine investigations are carried out. These often include estimation of creatinine clearance based on a 24h urine collection. Since January 1992, urea clearance, renal Kt/V and nPCR have been routinely estimated in every patient on whom an estimate of creatinine clearance was requested. Our clinical protocols do not include the prescription of dietary protein restriction.

Indications for dialysis initiation

Dialysis was initiated in response to uraemic symptoms which included general malaise, anorexia, nausea and vomiting, or because of fluid overload, not responsive to diuretics.

Dialysis patients

Haemodialysis programme. All patients were treated exclusively using high-flux synthetic membranes, predominantly polysulphone. Dialysers were reused using peracetic acid. Bicarbonate was used exclusively as the buffer. Ultrapure water was used for all dialysis procedures. Dialysis was prescribed and monitored using a two-pool kinetic model to ensure a Kt/V (renal plus dialysis) of 1.1–1.2 (per dialysis) for thrice weekly dialysis. Urea clearance and kinetic model to ensure a Kt/V (renal plus dialysis) of 1.1–1.2 was used:

\[
\text{K} = \frac{\text{A} \times \text{H} + \text{W}}{\text{V}}
\]

Total body water (V) was obtained from the Watson formula [18]:

\[
V = 1000 \left( 2.447 - 0.09516A + 0.1074H + 0.3362W \right) \text{ml (males)}
\]

\[
V = 1000 \left( -2.097 + 0.1069H + 0.2466W \right) \text{ml (females)}
\]

where \( A \) = age (years), \( H \) = height (cm), \( W \) = weight (kg).

The normalized urea clearance (Kt/V), where \( K = KRU \) (ml/min), \( t \) = number of min/day (min) and \( V \) = total body water (ml).

The nPCR [19]

\[\text{nPCR (g/kg/day) = 149.7 \times \frac{G/V}{V} + 0.17}\]

where \( G/V = U_v \times U_c/1440V \) \([U_v = \text{volume of 24h urine collection; } U_c = \text{urea concentration in 24h urine collection}.]

Serial biochemical data in the pre-dialysis group

Urea clearance and creatinine clearance were obtained from matched blood and 24 h urine specimens obtained at serial clinic visits prior to dialysis initiation. Protein excretion was also determined from the same 24h collections. The following parameters were derived for all patients studied.

- Total body water (V) was obtained from the Watson formula [18]:

\[
V = 1000 \left( 2.447 - 0.09516A + 0.1074H + 0.3362W \right) \text{ml (males)}
\]

\[
V = 1000 \left( -2.097 + 0.1069H + 0.2466W \right) \text{ml (females)}
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Serial data in dialysis patients

In haemodialysis (HD) patients, serial nPCR levels were recorded 1–3 times monthly based on pre- and post-dialysis blood urea estimations and estimates of urea concentration in interdialytic urine collections. The following formula was used:

\[\text{nPCR (g/kg/day) = 149.7 \times \frac{G/V}{V} + 0.17}\]

where \( G/V = [P_2(V + W)/V - P_1 + (U_v \times U_c/V)]/t_{id}; \ P_1 = \text{post-dialysis blood urea concentration dialysis 1 (mmol/L); } P_2 = \text{pre-dialysis blood urea concentration dialysis 2 (mmol/L); } W = \text{interdialytic weight gain (grams); } U_v = \text{volume of interdialytic urine collection (ml); } U_c = \text{urea concentration in interdialytic urine collection (mmol/L); } t_{id} = \text{interdialytic time interval (minutes).} \]
In CAPD patients, serial nPCR levels were recorded 3 monthly based on estimates of urea concentration in blood, 24 h urine collection and simultaneous spent dialysate collection. The following formula was used:

\[
\text{nPCR (g/kg/day) = } 149.7 \times \frac{G/V + 0.17}{1440V} \]  

where \(G/V = [(U_v \times U_c) + (D_v \times D_c)]/1440V\) \([U_v = \text{volume of 24 h urine collection}; U_c = \text{urea concentration in 24 h urine collection}; D_v = \text{volume of 24 h collection of spent dialysate}; D_c = \text{urea concentration in 24 h collection of spent dialysate}].

Biochemical measurements

Standard autoanalyser methods were employed. Urea was assayed by the urease reaction utilizing glutamate dehydrogenase. Creatinine was assayed by the Jaffe kinetic method.

Analysis of data

One-way analysis of variance (ANOVA) with post hoc Bonferroni test or Student’s t test were used as appropriate to compare groups with respect to continuous data. Categorical data were compared between groups using the \(\chi^2\) test with Yates’ correction and Fisher’s exact test as appropriate. Correlations were examined using the Pearson correlation coefficient. We analysed all pre-dialysis nPCR data to ascertain the relationship between nPCR and renal function. In patients who later started dialysis, we examined the univariate relationship between nPCR and survival using the Kaplan–Meier graph and log rank test. Cox regression analysis was carried out to investigate the effect of nPCR on survival corrected for age, diabetes, other co-morbidity (an 8-point scale as described previously [17]), functional capacity (Karnofsky performance score) and renal \(\text{Kt/V}_{\text{urea}}\) at dialysis initiation. All these statistical tests were performed using SPSS v11.0 (SPSS Inc., Chicago, IL). We also used non-linear regression analysis to examine the relationships between nPCR and various indices of renal function (Prism 4, Graphpad Software Inc., USA).

Results

Demographics

During the course of the study, 5082 measurements of nPCR were carried out in 1282 patients [group 1, mean age 55.1 years (SD 17.05); 778 (60.7%) male]. Two hundred and sixteen (16.8%) had nephrotic range proteinuria. Three hundred and sixty-one (28.2%) later developed end-stage renal failure and were included in the additional analysis of the effect of nPCR at initiation on dialysis outcome measures (group 3, mean age 59.1 years, SD 14.96; 64.8% male).

Correlations with nPCR

Mean nPCR in the pre-dialysis phase was 0.97 (SD 0.27). There were correlations between nPCR and creatinine clearance/1.73 m² \((r = 0.472, \ P < 0.001)\), urea clearance \((r = 0.481, \ P < 0.001)\) and \(\text{Kt/V}_{\text{urea}}\) \((r = 0.504, \ P < 0.001)\). nPCR correlated poorly with serum albumin \((r = 0.113, \ P < 0.001)\) and weakly and inversely with age \((r = -0.130, \ P < 0.001)\). The difference between mean nPCR in patients with and those without nephrotic range proteinuria was marginal and non-significant.

nPCR and renal function (cross-sectional analysis)

We examined the relationship between nPCR and creatinine clearance/1.73 m² performing a series of cross-sectional analyses.

Initially we compared mean nPCR values in groups of patients with varying degrees of renal impairment after the fashion of Ikizler et al. [7] When viewed in this fashion, nPCR appeared to fall steadily and significantly \((P < 0.001)\) as creatinine clearance/1.73 m² declined (Figure 1), falling from 1.17±0.31 in those with clearances >50 ml/min, to 1.04±0.27 in those whose clearance was 25–50 ml/min, to 0.93±0.21 at a clearance of 10–25 ml/min, and to 0.74±0.18 when the clearance had fallen to <10 ml/min. The mean nPCR level in each of these clearance groups was significantly different from mean levels in all other groups \((P < 0.001)\) by post hoc Bonferroni test. The same relationship persisted if only group 2 patients were considered (Figure 1 inset) except that the number of patients with values of creatinine clearance >50 was very small.

In spite of the significant linear correlations between nPCR and markers of renal function described above, inspection of scatterplots suggested that these relationships are non-linear. Non-linear regression analysis demonstrated that the best-fit curves took the form of a two-phase exponential association. Figure 2 demonstrates a similar relationship between nPCR and both creatinine and \(\text{Kt/V}_{\text{urea}}\) \((R^2 = 0.352)\). In both cases, there appears to be a gentle decline of nPCR as renal function falls, culminating in a dramatic increase in the rate of decline when the creatinine clearance has reached ~15 ml/min and the weekly \(\text{Kt/V}_{\text{urea}}\) 2.5. From Figure 2, it might be predicted that nPCR would fall to <0.8 at a creatinine clearance/1.73 m² of <9 ml/min and a weekly \(\text{Kt/V}_{\text{urea}}\) <1.6.

Temporal changes in nPCR

We examined changes in nPCR longitudinally with respect to time prior to dialysis initiation in those patients whose renal function declined to this point during the course of the study (group 2). Mean nPCR levels appeared to remain stable until an abrupt fall in the 3 months immediately before dialysis initiation (Figure 3). The time intervals compared were 3 months in the year prior to dialysis initiation, 6 months in the...
penultimate year before initiation, all values beyond 2 years being combined. This was to obtain comparable group sizes. The only value of mean nPCR which was different from any of its preceding values was the level in the 3 months prior to dialysis initiation, which was significantly less than all preceding values. The significance levels are shown in Figure 3.

nPCR groups

Since an nPCR (or nPNA) of <0.8 is taken as the marker of poor nutrition by DOQI and other authorities [11], we divided the patients into two groups according to whether their nPCR was above or below this cut-off point at the time of dialysis initiation. The last pre-dialysis nPCR was >0.8 in 171 (53.8%) and <0.8 in 147 (46.2%). The characteristics of these groups are shown in Table 1. Patients whose nPCR was <0.8 were slightly older (P<0.054), more dependent with a significantly lower Karnofsky performance score (P<0.001) and more uraemic with a significantly lower weekly Kt/V (P<0.001). In group 3 patients, once the dialysis started, there was a significant improvement in nPCR in the low initial nPCR group which was maximal during the first 15 months of treatment. All mean 3 monthly nPCR values obtained during this time were significantly higher than pre-dialysis values (P<0.001 in all cases). Thereafter, improvement in this group tailed off, such that most three monthly mean nPCR levels beyond 18 months were not significantly different from pre-dialysis levels (Figure 4). In the high nPCR group 3, monthly mean nPCR levels were maintained throughout the 36 month follow-up at pre-dialysis levels.

Fig. 1. Mean nPCR values in 1282 pre-dialysis patients (5082 samples) with varying degrees of renal impairment. (cross-sectional data). nPCR was significantly lower (P<0.001 by one-way ANOVA) at lower creatinine clearance/1.73 m² bands. The inset shows the same data in the 361 patients who started on dialysis during the course of the study.

Fig. 2. A total of 5082 nPCR values in 1282 pre-dialysis patients plotted against matched level of renal function, creatinine clearance/1.73 m² in the upper panel and Kt/Vurea in the lower panel. Best fit curves and equations displayed were calculated by non-linear regression analysis.
There were no significant differences between any of these mean three monthly levels and the mean pre-dialysis value. In addition, in all 3 month periods from pre-dialysis to 36 months post-initiation, mean nPCR levels were significantly higher in the high initial nPCR group than in the low initial nPCR group (Figure 4).

**Survival**

**Univariate analysis.** Follow-up was between 31 and 120 months, during which 152 patients (47.8%) died. Median survival of the whole cohort was 64 months. As expected [17], age, co-morbidity, functional capacity and diabetes were important predictors of survival (Table 2). A last pre-dialysis serum albumin level of <35 g/l, nPCR <0.8 and weekly Kt/Vurea <1.4 also predicted poor survival (Table 2). There were smaller but insignificant differences in survival at higher cut-off levels of both nPCR and Kt/Vurea. Median survival was 54.5 months in the group with creatinine clearance (per 1.73 m²) of <7.5 ml/min at the start of dialysis compared with 79.9 months in the ≥7.5 ml/min group (P = 0.01). Median survival was better in CAPD (intention to treat) than in HD patients (79.9 vs 58.3 months, P = 0.03), although this can be explained by CAPD patients being younger (mean age 56.5 vs 60.8 years, P = 0.013), less dependent (mean Karnofsky performance score 79.1 vs 70.8, P < 0.001) and having less co-morbidity (mean severity score 1.46 vs 2.27, P = 0.001). They also commenced dialysis at a higher weekly Kt/Vurea (mean 1.56 vs 1.38, P < 0.001) and had a slightly higher nPCR at commencement of dialysis (mean 0.838 vs 0.798, NS).

**Multivariate analysis.** The predictors of survival on the univariate analysis were used in Cox regression models. An nPCR of <0.8 predicted adverse survival (P = 0.015) when corrected for age, diabetes and other co-morbidity. Last pre-dialysis serum albumin was not a significant factor. The addition of Kt/Vurea to the model abolished this effect and Kt/Vurea became
a significant predictor \((P = 0.008)\). Age, diabetes and other co-morbidity remained significant factors \((P < 0.001\) in both models) (Table 3).

**Predictors of 1- and 2-year survival.** Using logistic regression analysis, the factors affecting 1-year survival were age (odds ratio 1.02 per year, \(P = 0.049\)), co-morbidity (odds ratio 1.53 per point, \(P < 0.001\)), weekly \(Kt/V_{urea}\) (odds ratio 0.45 per point, \(P = 0.041\)) and functional capacity (odds ratio 0.96 per point on Karnofsky performance score, \(P < 0.001\)). An nPCR of <0.8 was not a predictor of 1- or 2-year survival when corrected for the above factors.

**nPNA and nPCR**

Since a proportion of our patients had significant proteinuria, we re-analysed the data using nPNA
which also takes the urinary protein losses into account. There was a very high correlation ($r = 0.951$) between nPNA and nPCR. None of the results including survival analysis were significantly changed when nPNA was substituted for nPCR. The temporal changes in the nPNA in the pre-dialysis period (Figure 3b) were identical to those in nPCR (Figure 3a).

### Dialysis adequacy

The majority of patients were adequately dialysed. The mean total (dialysis + renal) $Kt/V$ was $2.21 \pm 0.47$ (per week) in PD patients; $1.25 \pm 0.21$ (two-pool) in three times per week HD patients; and $2.23 \pm 0.30$ (two-pool) in twice weekly HD patients. We examined the differences in dialysis adequacy between the low and high nPCR groups in thrice weekly HD and PD patients in the first, second, third and fourth year of dialysis (the number of twice weekly HD patients was small in year 1 and by year 4 only one patient was on twice weekly HD). There was no significant difference in $Kt/V$ between two groups except for PD patients in the first year of dialysis in whom $Kt/V$ was marginally higher in high nPCR ($2.38$ vs $2.25$; $P = 0.018$).

### Discussion

We have provided evidence that an abrupt decline in nPCR occurs late in the course of progressive CRF at a level of creatinine clearance/1.73 m$^2$ of <15 ml/min and at a weekly $Kt/V_{urea}$ of <2.5. We have also confirmed that nPCR at dialysis initiation is an important predictor of survival on dialysis even when corrected for age, the presence of diabetes and the non-renal co-morbid load, though it is not independent of the degree of uraemia at initiation. In addition, we have also shown that groups of patients started on dialysis with a normal nPCR tend to maintain this throughout the first 3 years on dialysis at least, whilst groups initiating with a low nPCR, though tending to improve initially, never match their normal nPCR counterparts throughout this period of follow-up. However, we cannot establish the cause and effect relationship between low nPCR and the clinical state in these patients.

We are less certain about what happens to nPCR earlier in the course of progressive CRF. When we looked at cross-sectional data, and plotted mean nPCR levels at different levels of creatinine clearance against the corresponding range of creatinine clearance (Figure 1), it appeared that the decline in nPCR began early in the course of CRF when creatinine clearance was as high as 50 ml/min. The findings replicated those of Ikizler et al. [7] However, when we looked at what happened to mean nPCR levels longitudinally as a function of time before dialysis initiation (Figure 3), it appeared that nPCR remained stable until very late in the course of CRF, the only significant change appearing in the 3 month period prior to dialysis initiation. The data from curve fitting provided some support for this latter interpretation, the best fits being obtained with two-phase exponential expressions, giving rise to a very gentle decline in nPCR throughout the course of progressive renal...
failure until very late in CRF when an abrupt decline took place (Figure 2).

Cross-sectional studies of the type shown in Figure 1, which suggest that the decline in mean nPCR begins early in the course of renal failure, are subject to a number of potential errors. The relationship between nPCR and creatinine clearance is highly complex. There is a genuine physiological association, with reduced renal function leading to reduced protein intake. Artefactual associations may also occur as the result of mathematical coupling. These may be of three broad types [21,22], error coupling, calculation bias and confounding. We think that the most significant of these in this situation is error coupling. This may arise because nPCR and creatinine clearance depend on common parameters, the most obvious of which is shared urine volume. Random errors in urine collection, volume measurement and sampling would affect both parameters in the same direction and to the same degree, thus inducing an artefactual positive correlation. Blood creatinine and urea measurements are carried out on the same autoanalyser run, a further potential source of error coupling. Confounding is the introduction of bias by extraneous factors associated with each of the study parameters. The fact that both nPCR and creatinine clearance are normalized by indices of body size (albeit different ones) may be a source of error. Calculation biases, in which random deviations in the parameters under study differ systematically from zero in particular situations, may have less of an effect in this situation. Expressing the mean nPCR data longitudinally, as a function of time prior to dialysis initiation, effectively excludes error coupling, and hence is likely to be a more reliable indicator of the actual behaviour of nPCR as renal function deteriorates.

Deteriorating nutritional status has been demonstrated early in renal failure in studies in which nutritional status and renal function were assessed by independent methods so were likely to be freer from bias of error coupling. In the largest of these [23], in which baseline glomerular filtration rate (GFR) determined by 121Iiothalamate clearance was correlated with baseline dietary and nutritional parameters estimated from diet records, biochemistry measurements and anthropometry, it was noted that the means of several nutritional parameters were successively less in groups with successively lower GFRs [≥37 (mild), 21–37 (moderate) and <21 ml/min/1.73 m² (severe)]. Few patients however, showed evidence of protein-energy malnutrition. The interpretation of these data is complicated by the fact that a significant proportion of patients were attempting to follow a protein-restricted diet even at baseline, and that the proportion of these was greater in the moderate and severe groups. In addition, it was noted that for several nutritional parameters, the rate of decline was greater at lower than at higher GFRs, which is consistent with the data presented here.

There are other problems in interpreting nPCR data. The use of nPCR as an indicator of protein intake is predicated on the steady state in which an amount of protein equivalent to the dietary intake is converted by liver to urea which is excreted by the kidney. Thus it becomes invalid as an indicator of protein intake during illness (catabolic state) and recuperation (anabolic state). It is dependent on normal liver function. Its use in pre-dialysis patients assumes that all the urea produced is excreted by the kidney and none is retained in the body, i.e. the blood urea is stable. A rise in blood urea results in an underestimation of nPCR. Other confounders include use of diuretics which may induce volume depletion, increased tubular re-absorption of urea and an increase in its blood concentration.

Despite these provisos, nPCR may be a useful tool in assessing nutritional status in patients with slowly progressive CRF. Maintenance of nutrition is an important aspect of preparation of patients for dialysis, and the findings presented here provide some support for monitoring this parameter among others in this circumstance with the aim of initiating dialysis before there is a catastrophic fall in nutritional status. Many factors, however, need to be taken into account. There is no panacea.

Conflict of interest statement. None declared.

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