Creatinine index and lean body mass are excellent predictors of long-term survival in haemodiafiltration patients

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Abstract

Background. No single measurement adequately defines protein-energy malnutrition. In the dialysis population, somatic protein mass, a useful marker of protein malnutrition, is estimated using the creatinine index (CI), lean body mass (LBM) or both, but the clinical usefulness of these indices remains uncertain. Moreover, calculating these indices requires formal creatinine kinetics or urine and dialysate collection. A simpler method to estimate the creatinine generation rate (G_Cr) probably might widen its use.

Methods. We evaluated the usefulness of creatinine-based indices for predicting mortality in a cohort of 226 French haemodiafiltration patients using the Cox proportional hazards method. We also proposed simple yet precise formulas to calculate post-dialysis creatinine (Cr_post) concentrations and derive creatinine generation rates (G_Cr) from readily available measures. These formulas were developed using a large database containing more than 10 000 measured Cr_post and G_Cr values based on formal creatinine modelling. A single set of monthly values was used to evaluate the validity of the formulas.

Results. When adjusted for comorbidities, sex and Kt/V, CI and LBM/body weight (LBM/BW) were better predictors of 5 year all-cause mortality than urea-based indices [survival relative risk (RR) = 0.24, P < 0.01 for CI < 22 mg/kg/day; RR = 0.33, P < 0.02 for LBM/BW < 0.75]. When the cohort was divided according to gender, similar results were found in males, but not in females. The different formulas allowed adequate prediction of Cr_post and G_Cr and classification of patients with good accuracy (CI < 22: sensitivity = 94%, specificity = 82%; LBM/BW < 0.75: sensitivity = 89%, specificity = 90%).

Conclusions. In a haemodiafiltration population, CI and LBM are excellent predictors of long-term survival. In anuric Caucasian haemodialysis patients, CI and LBM can be estimated from biochemical and anthropometric measurements without relying on formal modelling.

Keywords: creatinine index; end-stage renal disease; lean body mass; malnutrition; outcome predictors

Introduction

Malnutrition is an important predictor of mortality in the end-stage renal disease (ESRD) population. In stable patients, protein intake traditionally is estimated from the protein catabolic rate (PCR) or its equivalent, protein nitrogen appearance rate. Unfortunately, body mass index (BMI) or subjective global assessment scores provide a poor measure of protein-energy malnutrition (PEM). Serum creatinine and albumin can be determined easily and have been shown to be independent predictors of death [1].

Daily protein intake is mainly devoted to the preservation of muscle mass and body nitrogen reserves. For this reason, we strongly believe that creatinine-based indices should be among the tools used to evaluate PEM. In fact, lean body mass (LBM) estimation by creatinine kinetics [2] and the creatinine index (CI) [3] have already been shown to be useful markers of protein nutritional status, but their clinical usefulness as predictors of mortality remains to be clarified. In a cohort of French dialysis patients, the ratio observed/expected LBM was not found predictive of mortality when using a multivariate model [4]. A difficulty linked with the use of the creatinine-based indices is that they require formal creatinine kinetics modelling (CKM) or dialysate collection to compute the creatinine generation rate (G_Cr). LBM can be estimated by other methods. Dual-energy X-ray
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Subjects and methods

Data sources

The database used for this study relates to a group of prevalent and incident ESRD patients treated in two dialysis centres from the Montpellier (France) area since 1988, namely Lapeyronie Hospital (Montpellier) and the AIDER-Montpellier (Association pour l’Installation des Épurations Rénales; Clinique Jacques Mirouze), where monthly reviews of dialysis quantification have been performed for >15 years as part of the quality assurance processes. Since 1988, these data have been prospectively compiled in a database maintained in a personal computer, which contains data on 265 patients with ESRD treated for >3 months and includes more than 10 000 monthly entries describing formal UKM and formal CKM done on their mid-week dialysis sessions. The relevant laboratory analyses were performed on automated clinical counters (Beckman followed by Olympus), where creatinine determination was by enzymatic methods.

Calculations

For mortality analysis we used a cohort of 226 patients from the Montpellier region, treated by haemodiafiltration (HDF). A typical treatment consists of ultrapure, bicarbonate-based post-dilutional HDF with on-line production of reinjection fluid and ultrafiltration is between 18 and 24 litres per session. Membranes were reutilized between 1988 and 1994; since January 1995 only single use is allowed in France. In an effort to suppress the role of residual renal function, patients were included in the study no earlier than 1 year after starting dialysis. Since monthly measurements were available for the HDF cohort, the averages of the first 3 months were used for patients who were included in the study >1 year after their first dialysis, while the average of months −3, −2 and −1 before inclusion were used for incident patients. Comorbidities were evaluated with Khan’s index of comorbidity [9]. Briefly, patients were assigned to one of three categories (low, medium or high risk) based on age and the presence of vascular diseases (cardiac, cerebral, peripheral), diabetes, liver disease (hepatitis, cirrhosis, fibrosis), pulmonary impairment (chronic obstructive pulmonary disease, fibrosis) and cancer.

Formal CKM has been done at our institution for >15 years. We used data compiled since 1988 and had 10 278 values for Crpost-measured, GCr and CI for equation development. Crpost-measured was used to develop a first equation to predict post-dialysis creatinine concentration (Crpost-derived) from simple measurements. A second set of equations, which do not rely on modelling, was developed to calculate GCr from biochemical and anthropometric values. The validity of these equations was then evaluated on 28 anuric patients in our unit. Previously published formulas [2,3] for the calculation of CI and LBM were used to compute these values based on formula-derived GCr and kinetics-derived GCr. One set of monthly measurements (May 2003) was used to compare kinetics-derived and formula-derived GCr, CI and LBM.

Statistical analysis

For the cohort data, regression and Bland–Altman analyses were performed on serial data with GraphPad Prism version 4.00 for Windows® (GraphPad Software, San Diego, CA, USA, www.graphpad.com). Correlations were tested with regression analysis (least square method). For the predictive values, SAS 8.02 was used, the origin of the trend line being set at (0;0) (no constant term). P-values were calculated with analysis of variance and values of <0.05 were considered statistically significant. Mortality was analysed with SAS 8.02-generated Kaplan–Meier curves adjusted with the use of the Cox proportional hazards model.

Results

Urea-derived vs creatinine-derived indices as mortality predictors

The population used for mortality analysis is described in Table 1. The population appears to be representative of the French ESRD population with regards to the prevalence of diabetes, age, sex and race. The Cox proportional hazards model was adjusted for gender, Kt/V and Khan’s index of comorbidity. Current DOQI recommendations suggest a minimal single-pool Kt/V of 1.2 [10] and nPCR of 1.2 g/kg/day [11]. With these cut-off values, Kt/V and nPCR were not predictive of mortality, although a trend was detected for nPCR [relative risk (RR) = 0.62 (95% confidence interval: 0.34–1.16); data not shown]. For CI and LBM/body weight (LBM/BW), determination of cut-off values was based on clinical experience, but they correspond to the upper third of our cohort. For the entire population, CI and LBM/BW were excellent predictors of long-term survival when adjusted for gender, Kt/V and Khan’s index of
Post-dialysis creatinine concentration prediction

Post-dialysis creatinine prediction is well correlated with the urea reduction ratio ($\text{URR} = 1 - R$ where $R = \text{Urea}_{\text{post}}/\text{Urea}_{\text{pre}}$):

$$\text{Cr}_{\text{post}}(\text{mol/l}) = \text{Cr}_{\text{pre}} \times (1 - 0.857 \times \text{URR}) - 28$$

Values in the database were used to derive equation 1 and they allowed a good correlation between measured and formula-derived $\text{Cr}_{\text{post}}$ (Figure 2A) ($r^2 = 0.89$, $P < 0.001$; $n = 10278$). A Bland–Altman analysis (Figure 2B) showed that the mean prediction error for equation 1-derived creatinine concentrations was −32 μM. The determination factor in the Bland–Altman plot was insignificant ($r^2 = 0.041$). Logarithmic mean-based, time-averaged concentrations [$\text{TAC}_{\text{Crlm}} = \frac{\text{Cr}_{\text{pre}} \times (1 - \text{R}_{\text{Cr}})/\ln(\text{R}_{\text{Cr}})}{\text{BW}_{\text{post}}}$] and creatinine reduction ratio ($\text{CRR} = 1 - \text{R}_{\text{Cr}}$ where $\text{R}_{\text{Cr}} = \text{Cr}_{\text{post}}/\text{Cr}_{\text{pre}}$) were also highly correlated ($r^2 = 0.987$, $P < 0.001$ and $P < 0.001$) (data not shown).

Prediction of $G_{\text{Cr}}$

Our objective being the calculation of $G_{\text{Cr}}$, with readily available measurements, we postulated that, at equilibrium, $G_{\text{Cr}}$ would be proportional to the quantity of creatinine removed during dialysis ($\text{Cr}_{\text{pre}} \times \text{BW}_{\text{pre}} - \text{Cr}_{\text{post}} \times \text{BW}_{\text{post}}$). Since only muscle cells produce creatinine and obesity may have confounded the results, we adjusted for BMI. A good correlation between CKM-derived $G_{\text{Cr}}$ and the quantity of creatinine removed during dialysis was obtained with the use of a logarithmic mean and a correction factor for the BMI (25 for men and 22 for women). When $G_{\text{Cr}}$ was estimated with equations 2 and 3, a good correlation of statistical significance was found between $G_{\text{Cr, KM}}$ and $G_{\text{Cr, formula}}$ ($r^2 = 0.570$, $P < 0.001$; $n = 10026$). $G_{\text{Cr, formula}}$ was almost identical, regardless of whether $\text{Cr}_{\text{post}}$ was measured or deduced using equation 1 ($r^2 = 0.99$, $P < 0.001$; $n = 10026$). No correlation was found between URR and $G_{\text{Cr}}$ or CI ($r^2 = 0.04$ and 0.02, respectively).

$$G_{\text{Cr, male}} = 0.8 + (\text{BW}_{\text{pre}} \times \text{Cr}_{\text{pre}} - \text{BW}_{\text{post}} \times \text{Cr}_{\text{post}}) \times (1 - \text{R}_{\text{Cr}})/(- \ln(\text{R}_{\text{Cr}}) \times \text{BMI} \times 152)$$

$$G_{\text{Cr, female}} = 0.8 + (\text{BW}_{\text{pre}} \times \text{Cr}_{\text{pre}} - \text{BW}_{\text{post}} \times \text{Cr}_{\text{post}}) \times (1 - \text{R}_{\text{Cr}})/(- \ln(\text{R}_{\text{Cr}}) \times \text{BMI} \times 172.7)$$

Validation of the formulas

In order to estimate the precision of equations 1–3, results were compared with single measurements in 28 prevalent anuric patients without significant access recirculation. Those patients’ characteristics are depicted in Table 1. They are older, vintage is higher and diabetes is more prevalent, but this reflects a population of in-centre ESRD patients. Equation 1 allowed an excellent prediction of $\text{Cr}_{\text{post}}$ (data not shown) and $\text{TAC}_{\text{Crlm}}$ (Figure 3A) ($r^2 = 0.954$, $P < 0.001$ and $r^2 = 0.978$, $P < 0.001$, respectively). Bland–Altman analysis indicated that the mean prediction error was −9 μM (−46 to 28 μM) (Figure 3B). The correlation coefficient of the Bland–Altman analysis was insignificant. Estimating $G_{\text{Cr}}$ with equations 2 and 3 allowed calculation of the creatinine-based indices (equations 4 and 5, where BW is expressed in kg and $\text{TAC}_{\text{Crlm}}$ is in μmol/l).

$$\text{CI} (\text{mg/kg/day}) = 162.7 \times G_{\text{Cr, BW}} + 0.00429 \times \text{TAC}_{\text{Crlm}}$$

$$\text{LBMC} = 0.029 \times \text{CI} \times \text{BW}_{\text{post}} + 7.38$$

Once again, correlation was excellent whether $G_{\text{Cr}}$ was derived from formal CKM or with equations 1–3 (CI: $r^2 = 0.895$, $P < 0.001$; LBM: $r^2 = 0.932$, $P < 0.001$) (Figures 4A and 5A). Equations 2–4 allowed the detection of a CI <22 mg/kg/day with 94% sensitivity and 82% specificity while equations 2, 3 and 5 detected a LBM/BW of <0.75 with 88% sensitivity and 82% specificity (Figures 4B and 5B).
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Fig. 1. Kaplan–Meier plot with log-rank testing of male survival according to (A) baseline Cl (dashed line, Cl ≥ 22 mg/kg/day; full line, Cl < 22 mg/kg/day) and (B) baseline LBM/dry weight (dashed line, LBW/Wd ≥ 75; full line, LBW/Wd < 75).

### A
- **Survival**
- **Time (years)**
- **Censored**
- **Number at risk:**
  - C index < 0.22: 80 64 49 35 28 21
  - C index ≥ 0.22: 50 43 34 25 22 19

**RR** = 0.24 [0.08-0.69]
**p** = 0.008

### B
- **Survival**
- **Time (years)**
- **Censored**
- **Number at risk:**
  - LBM/BW < 0.75: 76 60 46 34 29 22
  - LBM/BW ≥ 0.75: 54 47 26 26 21 18

**RR** = 0.33 [0.14-0.81]
**p** = 0.015
Discussion

No single measurement can describe PEM in ESRD patients. One of the advantages of creatinine-based indices is that they reflect somatic protein metabolism. Since changes in the muscle mass are slow, CI also is more stable than nPCR, which is highly dependent on protein intake and dialysis dose. Finally, although albumin is well correlated with death, its inverse correlation with inflammation renders this parameter inaccurate regarding PEM. Some authors have correlated creatinine levels [12] with inflammation while others have not [13]. The former also describe an inverse relationship between nPCR and Crpre, which we could not reproduce with our data. Evaluation of PEM based on creatinine-derived indices is highly desirable to detect muscle mass wasting.

With 9.8/100 patient years, the total unadjusted mortality in our cohort is much lower than that reported in North America, but it is in accordance with mortality rates in the French ESRD population. The last DOQI guidelines for nutritional evaluation recommended that the CI and LBM associated with best survival and nutritional status should be defined. Our study clearly demonstrates that, among a male population, a CI of ≥22 mg/kg/day or an LBM/BW ratio of >75 or both are associated with lower all-cause mortality (RR = 0.24 and 0.33, respectively). Within this range, survival was >85% at 5 years. These results are consistent for the entire population, but most of the effect comes from the male population. The size of our cohort prohibits further subgroup analysis, so the male CI-threshold of 22 mg/kg/day should be viewed as directive for further research and not as a minimal or optimal value. In fact, target values for CI probably are different for males and females in different age groups. The absence of correlation among females...
could be due, apart from the insufficient power of our study, to the lack of association between somatic proteins and mortality as discussed recently by Stenvinkel et al. [14]. As in HIV-infected women who lose disproportionate amounts of fat during the course of their illness, muscle mass preservation may be due to different effects of sex hormones and could explain the lack of association between CI and mortality. Further research is needed in this area.

Unfortunately, most established approaches to assessing a body's protein status require CKM, which is not readily available in most dialysis facilities. In order to overcome this, we propose a simple and reliable way to estimate GCr, CI and LBM. The formulas to calculate TACr are based on the Crpost concentration. Prospective calculation will only require an extra blood sample at the end of dialysis. For retrospective analysis, if Crpost is missing, we also have developed a formula based on Crpre and URR (equation 1). This formula has been developed using a large database and shows excellent correlation. Similarly, the Bland–Altman analysis shows an adequate level of concordance and allows a good estimation of TACr. Equation 1 relies on Crpre and URR to estimate Crpost. Since creatinine elimination follows other small molecule clearance, this estimate should be applicable to almost everyone. This estimation is based on a single-pool model and does not account for rebound other than that from access and cardiopulmonary recirculation, but urea and creatinine have similar behaviour in terms of rebound.

Equations 2 and 3 have been developed based on mass balance, assuming that, at equilibrium, the creatinine generation rate equals the creatinine removal rate. The database used to develop these formulas contains more than 10 000 values for formal single-pool kinetics modelling of the creatinine generation rate. Estimates of GCr, CI and LBM were significantly correlated with those relying on formal CKM. The excellent correlation coefficient of GCr,KM vs the GCr formula (r²=0.90) in the validity analysis probably is due to the fact that, in the overall database (r²=0.57), some patients probably had residual renal function or vascular access recirculation or both, two conditions that were absent in our 28 prevalent patients. Our model is based on the assumption that creatinine elimination results from dialysis and endogenous degradation. Intestinal excretion and bacterial degradation of creatinine have been suggested as the avenues of endogenous elimination. The second term (0.00429 × TAC) in equation 4 reflects this decrement. Among patients with a residual renal function, urinary elimination

![Fig. 4. Preciseness of formal CKM vs formula-derived values for CI. (A) Linear regression analysis with constant term set to 0. Horizontal and vertical lines identify the cut-off value of 22 mg/kg/day. (B) Calculation of sensitivity (SENS), specificity (SPEC) and positive (PPV) and negative (NPV) predictive values. See the text for details regarding formulas.](image-url)
would also have to be added to our estimation of GCr. As a correction factor, we chose values of BMI associated with increased fat mass. The main reasons not to use urea volume or water volume (V) as a correction factor are that the original $r^2$ values of Watson’s formula [15] (0.70 for males and 0.73 for females) would have increased the magnitude of the error and that the objective of the formula was to avoid modelization.

On the other hand, racial differences exist in muscle mass. Shinzato et al. [16] also have published an equation to calculate CI without relying on creatinine kinetics. Their model was developed to fit a Japanese population. When applied to our Caucasian database and validation analysis, determination factors were less accurate ($r^2 = 0.46$ and 0.60 vs 0.57 and 0.90, respectively). The number of black patients in our cohort was small (<2%), which explains why we did not calculate a factor that would correct for their higher muscle mass. Therefore, our equation might underestimate GCr for black patients, but this is speculative and should be studied further. We therefore recommend using equations 2 and 3 for patients of Caucasian origin.

The CI calculated for our precision analysis averaged 19.5 mg/kg/day. If the fraction of endogenous degradation is excluded, creatinine production averages 18.7 mg/kg/day for males. This value exceeds Cockcroft and Gault’s estimation by 13% [17]. This can be explained by the fact that our correlation was based on GCrKM, which is known to result in values 10–20% above those of Mitch’s study [3,18]. Enhanced muscle catabolism in dialysis patients or a creatinine rebound effect (20–30%) are possible explanations, but at the moment the cause of this discrepancy has not been identified. Nevertheless, the high accuracy of the equations should permit the calculation of CI and LBM retrospectively in databases containing thousands of patients and should allow more subtle analysis.

In conclusion, we have shown that CI and LBM are excellent predictors of long-term survival in a cohort of French HDF patients. Since the CI and LBM reflect somatic proteins, we believe that these indices should be included in the panel used for the evaluation of protein-energy malnutrition. Hoping to stimulate further research, we developed simple and precise means to derive creatinine-based indices from readily available measurements. Optimal values remain to be described.

Conflict of interest statement. None declared.

References


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