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Retrospective Study

Reproducibility of serial creatinine excretion measurements in peritoneal dialysis

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Abstract

AIM

To test whether muscle mass evaluated by creatinine excretion (EX_{Cr}) is maintained in patients with end-stage kidney disease (ESKD) treated by peritoneal dialysis (PD), we evaluated repeated measurements of EX_{Cr} in a PD population.

METHODS

One hundred and sixty-six PD patients (94 male, 72 female) receiving the same PD dose for the duration of the study (up to approximately 2.5 years) had repeated determinations of total (in urine plus spent dialysate) 24-h EX_{Cr} (EX_{Cr} T) to assess the adequacy of PD by creatinine clearance. All 166 patients had two EX_{Cr} T determinations, 84 of the 166 patients had three EX_{Cr} T determinations and 44 of the 166 patients had four EX_{Cr} T measurements. EX_{Cr} T values were compared using the paired *t* test in the patients who had two studies and by repeated measures ANOVA in those who were studied three or four times.

RESULTS

In patients who were studied twice, with the first and second EX_{Cr} T measurements performed at 9.2 ± 15.2 mo and 17.4 ± 15.8 mo after onset of PD, respectively, EX_{Cr} T did not differ between the first and second study. In patients studied three times and whose final assessment occurred 24.7 ± 16.3 mo after initiating PD, EX_{Cr} T did not differ between the first and second study, but was significantly lower in the third study compared to the first study. In patients who were studied four times and whose fourth measurement was taken 31.9 ± 16.8 mo after onset of PD, EX_{Cr} T did not differ between any of the studies. The average EX_{Cr} T value did not change significantly, with the exception of the third study in the patients studied thrice. However, repeated determinations of EX_{Cr} T in individuals showed substantial variability, with approximately 50% of the repeated determinations being higher or lower than the first determination by 15% or more.

CONCLUSION

The average value of EX_{Cr} T remains relatively constant for up to 2.5 years of follow-up in PD patients who adhere to the same PD schedule. However, repeated individual EX_{Cr} T values vary considerably in a large proportion of the patients. Further studies are needed to evaluate the clinical significance of varying EX_{Cr} T values and the stability of EX_{Cr} T beyond 2.5 years of PD follow-up.

Key words: Creatinine excretion; Peritoneal dialysis; Lean body mass; Muscle mass

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Core tip: Total creatinine excretion (EX_{Cr}) in urine and in the used peritoneal dialysis (PD) fluid is correlated with muscle mass and has been shown to predict survival and morbidity of patients on PD. This retrospective study

evaluated the long-term constancy of 24-h excretion of creatinine in urine and spent peritoneal dialysate from patients with end-stage kidney disease treated by PD. Over a period of 2.5 years, the average value of total EX_{Cr} in the study population did not change significantly. However, in individuals there was a substantial variation of repeated measurements of total EX_{Cr} above or below its initial value. Approximately half of those studied repeatedly exhibited total EX_{Cr} above or below its initial value. Further studies are needed to evaluate changes, both increase and decrease, of EX_{Cr} in PD patients and the constancy of EX_{Cr} in patients on PD for more than 2.5 years.

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INTRODUCTION

An elevated serum creatinine concentration ($[Cr]_s$) is a predictor of prolonged survival in patients undergoing chronic peritoneal dialysis (PD)^[1]. $[Cr]_s$ is largely a function of muscle mass and is widely regarded as a reliable indicator of somatic nutrition. Exercising muscles secrete a variety of myokines with beneficial effects on various organ systems, including anti-inflammatory effects^[2]. Physical inactivity leads to altered pattern of myocyte secretion promoting obesity and atherogenesis^[2]. Inactivity is prominent among patients treated by chronic dialysis. McIntyre *et al.*^[3] reported a tendency to muscle mass depletion in this patient group. However, a significant limitation of $[Cr]_s$ as an indicator of somatic nutrition is reliance on this parameter as the sole determinant of muscle mass. In the steady state, which is defined as equal rates of creatinine production and elimination, $[Cr]_s$ has two physiological determinants, the rate of production of creatinine (P_{Cr}) which is a function of muscle mass, and the rate of removal of creatinine from body fluids, which is expressed as creatinine clearance (C_{Cr}). This relation is expressed as $[Cr]_s = P_{Cr}/C_{Cr}$. Consequently, variations in C_{Cr} in patients on PD can result in variations in $[Cr]_s$ that are unrelated to muscle mass^[4].

In the steady state, the total amount of creatinine excreted in spent PD dialysate plus urine over a certain time period (EX_{Cr} T) is in general a better index of muscle mass than $[Cr]_s$. Conditions in which EX_{Cr} T does not reflect muscle mass are addressed in the Discussion section of this report. EX_{Cr} T over 24 h was been proposed by Walser^[5] as an index of somatic nutrition in the general adult population and has been evaluated in PD populations. Whereas high EX_{Cr} T values are

associated with favorable outcomes, including survival and continued success of PD^[6,7], low values of $EX_{Cr} T$ are associated with a high risk of peritonitis and PD catheter-related infections^[8].

The lean body mass formula from creatinine production (LBM_{Cr}) in PD patients^[9] takes into account $EX_{Cr} T$ and creatinine eliminated through metabolic creatinine degradation (MCD), the second variable at a clearance of 0.038 L/kg^[10]. MCD per 24-h is calculated as $0.038 \times [Cr]_s$ (mg/mL) $\times 10 \times$ weight (kg). $EX_{Cr} T$ is invariably the larger of the two determinants of LBM_{Cr} . For example, in a 53-year old PD patient who weighs 70 kg and has a $[Cr]_s$ value of 9.5 mg/dL, estimated MCD rate will be 253 mg/24-h. Applying a PD population-specific formula predicting $EX_{Cr} T$ ^[11] to this illustrative example, average estimates of $EX_{Cr} T$, in mg/24-h, are 1062 if the patient is male and non-diabetic, 1023 if the patient is male and diabetic, 892 if the patient is female and non-diabetic and 852 if the patient is female and diabetic. High LBM_{Cr} values predict long survival of PD patients^[12-14].

The short-term reproducibility of $EX_{Cr} T$ in PD was studied by Lo and coauthors, who obtained two to four 24-h collections of urine and spent dialysate over a one-week interval from five patients undergoing PD^[15]. These authors reported maximal variations of $EX_{Cr} T$ from the mean ranging between 0.32% and 19.88%. The purpose of the present study was to investigate the reproducibility of $EX_{Cr} T$ in patients on long-term PD. Changes in renal function or peritoneal transport characteristics will change the amount of creatinine removed through each route. However, regardless of such changes steady state long-term constancy of $EX_{Cr} T$ is consistent with preservation of muscle mass in PD patients. In contrast, a progressive decrease in $EX_{Cr} T$ during PD would indicate progressive loss of muscle mass and deterioration of somatic nutrition.

MATERIALS AND METHODS

We analyzed creatinine excretion data collected during routine clearance measurements for assessment of the adequacy of PD. Patients included in this study were followed in Albuquerque during the years 1992 to 2002. Only patients in whom the prescribed dose of PD did not change during the observation period were included in the study. Approximately 40% of the patients were receiving continuous ambulatory peritoneal dialysis (CAPD) with four or five daily exchanges and 2.0-L or 2.5-L fill volume. The remaining patients received nocturnal automatic PD with 8-10 L fill volume plus one or two daytime PD exchanges with 2.0 L fill volume. Serum ($[Cr]_s$) at the study differed from the preceding or following monthly value by < 0.30 mg/dL in all patients. None of the patients were receiving drugs causing increased creatinine production (*e.g.*, fenofibrate).

The focus of the study was on detecting a statistically significant decline in $EX_{Cr} T$. The minimal number of patients required to detect a 15% reduction

in $EX_{Cr} T$ over time was calculated by power analysis. For a simple power analysis, we considered repeated measurements at two points in time and assumed a correlation of 0.7 between these two samples and a standard deviation of $EX_{Cr} T$ equal to 450 mg/24-h (see Tables in Results). The power and α value of the study were set at 80% and 0.05 respectively.

Between the sequential clearance studies we compared the following variables: Urine volume (V_u), drain volume (V_D), weekly Kt/V urea, weekly C_{Cr} , serum urea nitrogen level (SUN), $[Cr]_s$, EX_{Cr} in urine ($EX_{Cr} U$), EX_{Cr} in dialysate ($EX_{Cr} D$), and total creatinine excretion in urine plus dialysate ($EX_{Cr} T$).

Statistical analysis

Results are reported as mean \pm SD. Statistical comparisons were carried out using the two-tailed paired *t* test for patients with two clearance studies and the repeated measures ANOVA for patients who had three or four clearance studies. Statistical analysis was performed using SAS version 9.4.

RESULTS

Power analysis computed a minimal sample size of 37 patients for detecting a 15% decline in $EX_{Cr} T$. A total of 166 PD patients who had been subjected to at least two clearance studies comprised the initial study group. Among these patients, 84 patients had three clearance studies and 44 patients had four clearance studies. Small number of patients, eight or less, underwent five or more studies. Consequently, this study includes patients who had two, three and four clearance studies.

Table 1 summarizes relevant features of the patients included in the report. There were no significant differences between the three subgroups in terms of the age of patients at the onset of PD, percent of males and females or percent of patients with end-stage renal disease secondary to diabetic nephropathy.

Table 2 compares variables related to creatinine excretion in patients with two clearance studies. Between the first and second clearance study V_u , total Kt/V urea, total C_{Cr} , and $EX_{Cr} U$ decreased, $[Cr]_s$ and $EX_{Cr} D$ increased, while V_D , SUN and $EX_{Cr} T$ did not change significantly. Peritoneal C_{Cr} did not change while renal C_{Cr} decreased from the first to the second study. Average peritoneal ($C_{Cr} P$) and renal ($C_{Cr} R$) weekly C_{Cr} , expressed in L/1.73 m² throughout this report, values were as follows: $C_{Cr} P$ 48.7 in the first and 49.5 in the second study; $C_{Cr} R$ 29.1 in the first and 18.4 in the second study.

Table 3 compares variables in patients who were studied three times. V_u , total Kt/V urea, total C_{Cr} and $EX_{Cr} U$ decreased progressively from the first to the third measurement, while $EX_{Cr} T$ was significantly lower in the third study than in the first study. V_D and SUN did not change, while $[Cr]_s$ increased; however, the increasing trend in $EX_{Cr} D$ did not reach statistical significance. Peritoneal C_{Cr} did not change while renal

Table 1 Patient characteristics *n* (%)

| | Two clearance studies | Three clearance studies | Four clearance studies |
|---|-----------------------|-------------------------|------------------------|
| Patient number | 166 | 84 | 44 |
| Age at onset of peritoneal dialysis, yr | 52 ± 15 | 51 ± 16 | 51 ± 18 |
| Male | 94 (56.6) | 46 (54.8) | 26 (59.1) |
| Female | 72 (43.4) | 38 (45.2) | 18 (40.9) |
| Diabetic nephropathy | 73 (44.0) | 36 (42.9) | 17 (38.6) |

Table 2 Creatinine excretion in patients with two studies

| Variable | 1 st clearance study | 2 nd clearance study | <i>P</i> value |
|--|---------------------------------|---------------------------------|----------------|
| PD duration, mo | 9.2 ± 15.2 | 17.4 ± 15.8 | |
| VU, L/24-h | 0.54 ± 0.63 | 0.40 ± 0.53 | < 0.001 |
| VD, L/24-h | 11.3 ± 3.2 | 12.1 ± 3.6 | NS |
| Kt/V urea, weekly | 2.30 ± 0.62 | 2.12 ± 0.03 | 0.003 |
| C _{cr} , L/1.73 m ² , weekly | 77.9 ± 32.1 | 67.9 ± 18.2 | 0.002 |
| SUN, mg/dL | 49.7 ± 15.1 | 49.4 ± 16.2 | NS |
| [Cr] _s , mg/dL | 9.1 ± 3.3 | 10.1 ± 3.4 | 0.001 |
| EX _{cr} U, mg/24-h | 406 ± 337 | 286 ± 350 | 0.003 |
| EX _{cr} D, mg/24-h | 680 ± 337 | 769 ± 390 | < 0.001 |
| EX _{cr} T, mg/24-h | 1087 ± 470 | 1055 ± 421 | NS |

PD: Peritoneal dialysis; NS: Not significant; VU: Urine volume; VD: Drained volume of spent dialysate; Kt/V urea: Fractional urea clearance, weekly; C_{cr}: Weekly renal plus peritoneal creatinine clearance; SUN: Serum urea nitrogen; [Cr]_s: Serum creatinine concentration; EX_{cr} D: Creatinine excretion in spent dialysate; EX_{cr} U: Creatinine excretion in urine; EX_{cr} T: Total creatinine excretion in urine plus dialysate.

C_{cr} decreased progressively from the first to the third study. Average weekly C_{cr} P and C_{cr} R values were as follows: C_{cr} P 50.5 in the first, 48.2 in the second and 49.7 in the third study; C_{cr} R 28.8 in the first, 23.2 in the second and 18.3 L/1.73 m² in the third study.

Table 4 compares clearances and creatinine excretion parameters in patients who had four clearance studies. V_u, total Kt/V urea and total C_{cr} decreased progressively from the first to the fourth determination. EX_{cr} U decreased significantly between the first and third studies, but reached a stable mean between the third and fourth studies. [Cr]_s increased progressively from the first to the third study; however, the mean values were not different between in the third and fourth studies. V_d and SUN were essentially the same in the four studies. EX_{cr} D increased progressively from the first to the fourth study, whereas EX_{cr} T did not change significantly throughout the study. Peritoneal C_{cr} did not change while renal C_{cr} decreased progressively from the first to the fourth study. Average weekly C_{cr} P and C_{cr} R values were as follows: C_{cr} P 50.2 in the first, 47.4 in the second, 51.2 in the third and 49.7 in the fourth study; C_{cr} R 27.3 in the first, 23.0 in the second, 17.3 in the third and 16.4 L/1.73 m² in the fourth study.

Table 5 shows the results (number and percent) of the second, third and fourth studies where EX_{cr}

Table 3 Creatinine excretion in patients with three studies

| Variable | 1 st clearance study | 2 nd clearance study | 3 rd clearance study | <i>P</i> value |
|--|---------------------------------|---------------------------------|---------------------------------|-----------------|
| PD duration, mo | 8.6 ± 7.8 | 16.8 ± 11.6 | 24.7 ± 16.3 | |
| VU, L/24-h | 0.58 ± 0.66 | 0.45 ± 0.59 | 0.38 ± 0.50 | 0.0001 |
| VD, L/24-h | 11.5 ± 4.0 | 11.8 ± 3.7 | 12.4 ± 3.7 | NS |
| Kt/V urea, weekly | 2.28 ± 0.65 | 2.14 ± 0.58 | 2.12 ± 0.63 | 0.0245 |
| C _{cr} , L/1.73 m ² , weekly | 79.3 ± 35.6 | 71.4 ± 27.8 | 68.0 ± 26.9 | 0.0335 |
| SUN, mg/dL | 50.4 ± 18.5 | 49.5 ± 17.9 | 49.2 ± 19.2 | NS |
| [Cr] _s , mg/dL | 9.5 ± 3.5 | 9.8 ± 3.4 | 10.1 ± 3.3 | 0.0066 |
| EX _{cr} U, mg/24-h | 418 ± 404 | 370 ± 425 | 286 ± 362 | < 0.0001 |
| EX _{cr} D, mg/24-h | 731 ± 379 | 767 ± 396 | 779 ± 382 | NS ¹ |
| EX _{cr} T, mg/24-h | 1149 ± 416 | 1137 ± 454 | 1065 ± 442 | 0.0087 |

¹Statistical trend (*P* = 0.0895). PD: Peritoneal dialysis; NS: Not significant; VU: Urine volume; VD: Drained volume of spent dialysate; Kt/V urea: Fractional urea clearance, weekly; C_{cr}: Weekly renal plus peritoneal creatinine clearance; SUN: Serum urea nitrogen; [Cr]_s: Serum creatinine concentration; EX_{cr} D: Creatinine excretion in spent dialysate; EX_{cr} U: Creatinine excretion in urine; EX_{cr} T: Total creatinine excretion in urine plus dialysate.

T differed from the EX_{cr} T of the first study by less than 15%. The same table also shows the number and percent of studies with EX_{cr} T higher or lower than the EX_{cr} T of the first study by 15% or more. In approximately half of the second, third and fourth studies EX_{cr} T differed from the first study by less than 15%. In 25.0%-33.3% of the patients, EX_{cr} T values in subsequent studies were higher than the EX_{cr} T value found in the first study by more than 15%. In 19.1%-21.1% of the patients, EX_{cr} T in subsequent studies was lower than the EX_{cr} T in the first study by more than 15%.

DISCUSSION

This study had two important findings: First the mean EX_{cr} T value did not change significantly in 2.5 years of follow-up of patients who were on the same PD schedule for the duration of the study, with the exception of a lower mean EX_{cr} T in the third study than in the first study in EX_{cr} data analyzed thrice. The constancy of the mean EX_{cr} T was maintained despite a progressive decrease in urinary volume, urinary C_{cr} and urinary EX_{cr}. Increases in peritoneal EX_{cr} associated with parallel rises in [Cr]_s offset the declines in renal EX_{cr}. Second, in about half of the patients, individual values of EX_{cr} T varied substantially in clearance studies following the initial study. These findings have important clinical implications.

The finding of unchanged EX_{cr} T suggests that the muscle mass of the average patient who remains on PD for 2.5 years is preserved. This observation points to stable creatinine production, and preserved muscle mass, as favorable predictors of outcomes of PD; however, this issue will require further investigation. The finding of great variation of individual EX_{cr} T values on repeated measurements should prompt investigation of the factors affecting EX_{cr} T in PD in addition to changes

Table 4 Creatinine excretion in patients with four clearance studies

| Variable | 1 st clearance study | 2 nd clearance study | 3 rd clearance study | 4 th clearance study | P value |
|--|---------------------------------|---------------------------------|---------------------------------|---------------------------------|----------|
| PD duration, mo | 8.1 ± 12.6 | 16.5 ± 4.4 | 24.5 ± 16.3 | 31.9 ± 16.8 | |
| VU, L/24-h | 0.54 ± 0.55 | 0.41 ± 0.49 | 0.33 ± 0.40 | 0.29 ± 0.42 | < 0.0001 |
| VD, L/24-h | 11.8 ± 3.9 | 12.2 ± 3.6 | 12.2 ± 3.5 | 12.5 ± 3.2 | NS |
| Kt/V urea, weekly | 2.27 ± 0.65 | 2.15 ± 0.56 | 2.13 ± 0.54 | 2.10 ± 0.55 | 0.0356 |
| C _{Cr} , L/1.73 m ² , weekly | 77.5 ± 29.7 | 70.4 ± 28.5 | 68.5 ± 25.7 | 66.1 ± 22.1 | 0.0238 |
| SUN, mg/dL | 49.8 ± 16.7 | 49.5 ± 15.4 | 49.2 ± 15.3 | 49.0 ± 13.5 | NS |
| [Cr] _s , mg/dL | 9.8 ± 3.6 | 10.2 ± 3.7 | 10.8 ± 3.8 | 10.8 ± 3.6 | 0.0009 |
| EX _{Cr} U, mg/24-h | 411 ± 438 | 382 ± 460 | 272 ± 345 | 282 ± 481 | 0.0011 |
| EX _{Cr} D, mg/24-h | 755 ± 406 | 788 ± 424 | 808 ± 438 | 853 ± 398 | 0.0021 |
| EX _{Cr} T, mg/24-h | 1166 ± 440 | 1170 ± 495 | 1080 ± 455 | 1135 ± 521 | NS |

PD: Peritoneal dialysis; NS: Not significant; VU: Urine volume; VD: Drained volume of spent dialysate; Kt/V urea: Fractional urea clearance, weekly; C_{Cr}: Weekly renal plus peritoneal creatinine clearance; SUN: Serum urea nitrogen; [Cr]_s: Serum creatinine concentration; EX_{Cr} D: Creatinine excretion in spent dialysate; EX_{Cr} U: Creatinine excretion in urine; EX_{Cr} T: Total creatinine excretion in urine plus dialysate.

Table 5 Number (percent) of studies with creatinine excretion deviating from baseline by < 15% and ≥ 15%

| Study | < 15% from the 1 st study | ≥ 15% above the 1 st study | ≥ 15% below the 1 st study |
|--------|--------------------------------------|---------------------------------------|---------------------------------------|
| Second | 90 (54.2%) | 41 (24.7%) | 35 (21.1%) |
| Third | 40 (47.6%) | 28 (33.3%) | 16 (19.1%) |
| Fourth | 24 (54.5%) | 11 (25.0%) | 9 (20.5%) |

in the muscle mass.

One factor that can affect EX_{Cr} T is a change in total C_{Cr}. Mitch and Walser computed a “metabolic” C_{Cr} equal to 0.038 L/kg per 24-h in patients with renal failure mediated primarily by creatinine elimination through the gastrointestinal tract^[16]. As [Cr]_s levels increase progressively in advancing renal failure, the amount of creatinine removed through the metabolic-route increases progressively with a concomitant decrease in the measured renal EX_{Cr}^[16].

Large increases in total C_{Cr} in PD patients lead in the steady state to drop in [Cr]_s and in creatinine removal by the “metabolic” route and increase in EX_{Cr} T. In a previous study, we noted an increase in EX_{Cr} T in PD patients whose measured total (peritoneal plus renal) C_{Cr} was increased, with proportional decrease in [Cr]_s, following prescribed increases in the PD dose^[17]. This was the reason for including in the present study only patients with unchanged PD schedules. No effect of the decrease in total C_{Cr} through loss of renal function on EX_{Cr} T was seen in this study even when total C_{Cr} decreased by 11.4 L/1.73 m² weekly, on the average, between the first and fourth measurements (Table 4). We suggest that the increase in the amount of creatinine removed by the metabolic route due to the rise in [Cr]_s between these two measurements was too small to be detected by our statistical analysis. On average, [Cr]_s rose by 1.0 mg/dL between the first and fourth clearance study (Table 4). With this degree of increase in [Cr]_s, the rise in the amount of creatinine removed through the metabolic route at a C_{Cr} of 0.038 L/kg per 24-h would be only 26.6 mg/24-h in an individual weighing 70 kg.

Creatinine is formed by non-enzymatic breakdown of creatine-phosphate. Variations in the rate of creatine-phosphate conversion to creatinine may cause changes in EX_{Cr} T that are independent of changes in muscle mass. Neuromuscular diseases^[18] and the stage of recovery from protein malnutrition^[19] are examples of conditions characterized by abnormal creatine metabolism which leads to dissociation between creatinine production and muscle mass. In addition, neuromuscular diseases affect creatinine production and excretion through their effect on muscle mass homeostasis. The loss of muscle mass secondary to chronic neuromuscular disease is one of the major causes of decreases in creatinine production and EX_{Cr} T. Acute muscular disease, (e.g., rhabdomyolysis) however, increases creatinine production. Rhabdomyolysis can result from disease, poisons and medications exemplified by lipid-lowering agents^[20]. Other conditions causing increases in creatinine production and EX_{Cr} T include pregnancy^[21], consumption of meat and intense exercise^[22].

Circumstances that raise EX_{Cr} T without affecting creatinine production include errors in the collection of urine and spent dialysate and the presence of a non-steady state. Non-steady state following a rapid rise in C_{Cr} will increase EX_{Cr} T and decrease [Cr]_s. A hemodialysis session represents such a non-steady state condition. PD patients, who are non-compliant with their PD prescription and resume the prescribed PD schedule on the day of a clearance study will manifest a similar non-steady state. A high value of measured EX_{Cr} T over the EX_{Cr} T predicted by the Cockcroft-Gault formula^[23] (M/P_{Cr}) was proposed as a means of identifying non-compliance in PD^[24]. Although some

studies supported the use of the M/P_{Cr} ratio as a means of detecting PD non-compliance^[25,26], several reports confirmed that the sensitivity of this test is poor^[27-32]. Nevertheless, noncompliance will invariably increase EX_{Cr} T on the first day of resumption of the prescribed PD schedule^[28] and can be an important cause of the variation of EX_{Cr} T.

Conditions that can potentially lead to low EX_{Cr} T values include decreased production of creatinine, urine and dialysate collection errors, and intercurrent acute illnesses. This last category has not been studied adequately in PD patients. In acute illness, creatinine production could be temporally increased because of muscle disease or decreased because of loss of muscle mass. In one study, PD-associated peritonitis with routine course resulted in a 2.3% drop in body weight and 7.8% drop in [Cr]_s, while peritonitis with a protracted course resulted in a 7.2% drop in body weight and 25.0% drop in [Cr]_s^[33]. These findings suggest a loss of muscle mass proportional to the duration of peritonitis. However, an increase in peritoneal C_{Cr} secondary to peritoneal membrane inflammation could also cause a drop in [Cr]_s. EX_{Cr} data, which would allow differentiation between a rise in C_{Cr} and a loss of muscle mass as the cause of the decrease in [Cr]_s were not provided in this study. The effects of acute illness on EX_{Cr} in PD will need further studies.

A final consequence of all the aforementioned influences on EX_{Cr} T is their effect on the estimation of LBM_{Cr}. Two studies reported agreement between LBM_{Cr} and estimation of lean body mass by research methodologies^[34,35]. Another study suggested that determination of lean body mass as LBM_{Cr} has advantages over its determination by bioimpedance or dual energy X-ray absorptiometry in overhydrated PD patients^[36]. However, several studies have reported substantial differences between LBM_{Cr} and other methods used to assess muscle mass and between LBM_{Cr} and other indices of nutrition in PD patients^[35,37-42]. Nevertheless, one of these studies did support the monitoring of EX_{Cr} T as a means of assessing changes in muscle mass^[37].

Our study has limitations: First, selection bias could have led to the finding of stable creatinine excretion with stable patients remaining on PD for longer time. Related to this limitation, clinical information and data on other indices of nutrition associated with the observed changes in EX_{Cr} T were not available for analysis. Second, the data available to us do not allow us to address whether any of the known determinants of creatinine excretion in patients treated by PD (body weight, age, gender, and diabetic status) can predict a decrease or increase in their EX_{Cr} T. Finally, monitoring of EX_{Cr} T beyond 2.5 years after initiation of PD was not performed because of the small number of such subjects. Future studies should address these limitations.

In conclusion, average EX_{Cr} T remains stable for up to 2.5 years in patients who are maintained on the

same PD schedule, despite a progressive loss of residual renal function which causes a progressive decline in urinary flow rate, C_{Cr} and EX_{Cr}. This finding suggests that the muscle mass of the average patient who remains on PD during this same time period is preserved. However, many patients exhibit substantial variability of EX_{Cr} T in sequential measurements. Both increases and decreases in EX_{Cr} T of individual patients managed by PD call for a systematic search for the conditions responsible for these changes. Further studies are also needed to evaluate the stability of EX_{Cr} T beyond 2.5 years of PD and the potential associations of changes in EX_{Cr} T with clinical outcomes and other indices of nutrition.

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COMMENTS

Background

In the steady state, defined as equal rates of production and removal, creatinine excretion reflects muscle mass. Loss of muscle mass has adverse effects on the outcomes of patients with chronic diseases, including patients with end-stage kidney disease treated by peritoneal dialysis (PD). High levels of creatinine excretion are associated with favorable outcomes in this patient population. The prevalence of adverse influences (*e.g.*, inactivity, chronic inflammatory state) in PD populations suggests loss of muscle mass in long-term PD. Repeated measurement of creatinine excretion in patients on long-term PD, which represents a steady state, provide a means of monitoring muscle mass.

Research frontiers

Muscle mass can be evaluated by several research methods. These methods require expenses and added expertise of the research personnel and, therefore, are not suitable for routine monitoring of PD populations.

Innovations and breakthroughs

Repeated measuring of total excretion of creatinine in spent peritoneal dialysate and urine offers a way of monitoring muscle mass in PD patients. Creatinine excretion measurements have been performed as part of monitoring adequacy of azotemic indices removal in PD. Comparison of subsequent creatinine excretion measurements to the first measurement, as used in this study, is simple and does not require added expenses.

Applications

The methodology explored in this report is appropriate for monitoring patients on long-term PD and for evaluating interventions (*e.g.*, exercise, diet) directed towards preserving or improving muscle mass in these patients.

Terminology

The following abbreviations express the technique for monitoring creatinine excretion in PD: EX_{Cr} U = urinary creatinine excretion, mg/24-h; EX_{Cr} D = creatinine excretion in spent peritoneal dialysate, mg/24h; EX_{Cr} T = EX_{Cr} U + EX_{Cr} D.

Peer-review

In this manuscript, the authors describe the reproducibility of serial creatinine excretion measurements in PD patients. They concluded that the average total creatinine excretion in urine plus dialysate (EX_{Cr} T) remains stable for up to 2.5

years in patients who are maintained on the same PD schedule, despite the progressive loss of residual renal function which causes a progressive decline in the urinary flow rate, renal plus peritoneal creatinine clearance (Ccr), and creatinine excretion (EXcr). They also suggested that the muscle mass was preserved in the average patient who remained on PD during this time period. This paper is clinically interesting.

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