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ORIGINAL ARTICLE

Evolution of renal function in patients with severe intestinal failure on home parenteral nutrition

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ABSTRACT

Background. Kidney disease is a frequent but underestimated complication in patients suffering from intestinal failure (IF) treated by long-term home parenteral nutrition (HPN). The evolution in glomerular filtration rate (GFR) over time is poorly characterized. The current equations for estimating GFR have limited precision. No study has specifically investigated the reliability of recent creatinine-based estimated GFR (eGFR) equations in this population. The aim of this study was to evaluate the renal function decline under home parenteral nutrition (HPN) with a gold standard method and compare the performances of routinely used eGFR equations.

Methods. Forty patients with HPN and two or more GFR measurements were retrospectively studied. The renal function decline was calculated by the slope drawn between the successive measured GFRs (mGFRs). The performances of the Modification of Diet in Renal Disease, Chronic Kidney Disease Epidemiology Collaboration, full age spectrum and revised Lund–Malmö equations were compared with reference methods (inulin or iohexol clearance).

Results. The mean mGFR was 78 ± 28 mL/min/1.73 m^2. The annual decline of mGFR was −1.9 mL/min/1.73 m^2/year. No predisposing factor was identified to predict impairment in renal function. eGFR formulas grossly overestimated mGFR and had a low level of accuracy.

Conclusions. Patients with IF are at significant risk for impaired renal function. In this population, the tested eGFR equations were inaccurate. However, monitoring kidney function with mGFR remains important in these patients, as their GFR regularly declines and no specific risk factor has yet been identified.

Keywords: chronic renal failure, home parenteral nutrition, intestinal failure, measured glomerular filtration rate

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INTRODUCTION

Intestinal failure (IF) results from the reduction of gut function below the minimum necessary to maintain macronutrients, water and electrolyte balance [1]. It is a highly disabling condition chiefly the result of massive intestinal loss caused by surgery, trauma or infarction. Patients with irreversible IF require long-term home parenteral nutrition (HPN) to maintain health and/or growth. First used in the 1970s, HPN has significantly improved the prognosis of these patients, allowing them to reach a 70–80% survival rate after 5 years of treatment [2]. However, this technique is still associated with various complications, including catheter infections and thrombosis, liver disturbances and bone disease. Few studies have described renal function impairment in this population. Indeed, patients with IF are at persistent risk for hypovolaemia and electrolyte imbalance due to impaired absorption and increased intestinal losses, nephrocalcinosis and chronic deposition of oxalate crystals, nephrotoxic medications and inflammation, all of which may have an adverse effect on kidney function [3–9].

Two cross-sectional studies reported decreased renal function in about half of HPN adult patients [6, 7]. No relationship was found with the number of infections, the use of nephrotoxic antibiotics or the amount of protein administered [6, 7]. Lauverjat *et al.* [6] described a lower urinary sodium:potassium (Na:K) ratio and a higher level of serum renin and aldosterone in 21 patients with a decreased measured glomerular filtration rate (mGFR), indicating that chronic dehydration may be responsible for renal impairment. Buchman *et al.* [4] reported a decrease in creatinine clearance of 3.5% per year in a retrospective cohort of 33 adult patients. This unfavourable evolution was confirmed in a recent study in 33 patients presenting an annual decline in estimated GFR (eGFR) of 2.8% [9]. However, renal function was estimated instead of directly measured and, until now, no study has monitored renal function by mGFR in patients on HPN.

Because patients with IF have singular characteristics in terms of age, nutritional state, metabolic profile, muscle mass, medications and comorbidities, creatinine-based eGFR equations may be subject to important caveats. The gold standard method for mGFR is the urinary clearance of inulin during continuous intravenous infusion. To simplify the procedure, a number of alternative clearance methods and filtration markers (^{51}Cr-EDTA, iohexol or iothalamate) are routinely used in some specialized centres. However, these measurements require the same degree of rigor as those needed for calibration issues, which may not be available in all hospitals. This is why mathematical creatinine-based eGFR was developed. Today, the simplified Modification of Diet in Renal Disease (MDRD) Study [10] and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [11] equations are the most widely used for GFR estimation. New formulas are still being developed in order to estimate GFR with the greatest possible confidence: the full age spectrum (FAS) equation [12] aims to overcome the lack of continuity between ages, while the revised Lund–Malmö (RLM) equation [13] could show better accuracy for CKD Stages 4–5. However, these formulas were never validated in the present population.

The aim of this study was to determine whether the use of HPN is associated with a decrease in mGFR during follow-up, assess the risk factors that might contribute to renal function decline and evaluate the accuracy of different formulas estimating GFR in this population compared with the reference method.

MATERIALS AND METHODS

Patients

This study included patients with IF treated with HPN who were followed up at the Intensive Nutrition Center in Lyon Sud University Hospital, Pierre-Bénite, France, between January 1998 and March 2018. The local ethical committee approved the use of patients' information and the study protocol was conducted in accordance with ethical standards and the principles of the second Declaration of Helsinki. The French 'Comité National de l'Informatique et des Libertés' was notified and data were collected in accordance with French law. All patients were informed of the study.

Every patient receiving HPN for >6 months and whose GFR was measured at least twice separated by a minimum of 1 year were included. Age, gender, body mass index (BMI; body weight in kilograms/height in square metres), primary disease and cause of IF, history of high blood pressure, type 2 diabetes, renal lithiasis and renal disease were recorded for all patients. The characteristics of the HPN programme including nutritional bag volume and composition (sodium concentration and amino acid content) and number of infusions per week were collected. To precisely assess the digestive status, we registered the length of remnant bowel and the presence, or not, of a stoma and right colon.

GFR measurements

GFR measurements were performed using gold standard methods—urinary inulin or plasma iohexol clearance—depending on the clinical status of the patient as previously reported [14]. Briefly, the renal clearance of inulin (polyfructosan, Inutest; Fresenius Kabi, Graz, Austria) was performed by trained staff members during a continuous infusion after a priming dose (30 mg/kg) of polyfructosan. Water diuresis was induced by oral administration of 5 mL/kg of water followed by 3 mL/kg every 30 min combined with an intravenous infusion of 0.9% sodium chloride. This enabled the patients to spontaneously empty their bladder every 30 min. Three to four urine samples were collected and a blood sample was drawn midway through each collection period. Inulin clearance was calculated using the standard UV/P formula (urinary inulin × urine flow/plasma inulin). Plasma and urine polyfructosan measurements were performed using an enzymatic method [15]. Iohexol plasma clearance was calculated from the slope of plasma concentration using a one-compartment model corrected using the Bröchner-Mortensen method [16]. Iohexol of 6 mL (Omnipaque, 300 mg/mL; GE Healthcare, Chicago, IL, USA) was administered and blood samples were drawn from the contralateral arm after 120, 180, 240 and 300 min (if eGFR <30 mL/min/1.73 m^2). The plasma iohexol concentration was measured by high-performance liquid chromatography [17].

The results of mGFR were normalized to 1.73 m^2 of body surface area (BSA) according to the Dubois equation [18] in the main analysis. Urine was collected over 24 h at the time of each GFR measurement and diuresis, microalbuminuria, creatininuria, tubular reabsorption rate of sodium and chloride were measured. Urine osmolality was measured in the morning urine. When 24-h urinary collection was complete, urinary creatinine clearance was calculated.

GFR estimation and creatinine assay

In each patient, creatinine and mGFR were performed the same morning. All creatinine measurements were performed in the Lyon Sud hospital laboratory. Before 8 June 2009, plasma

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Table 1. Overview of equations used in this comparison study, with reference to the original publication

Name (reference)		Equation
MDRD 2006 [10]	♂	$GFR = 175 \times (SCr \times 0.0113)^{-1.154} \times age^{-0.203} \times$ [1212 if African American origin] (SCr in μmol/L)
(IDMS calibration)	♀	$GFR = 175 \times (SCr \times 0.0113)^{-1.154} \times age^{-0.203} \times 0.742 \times$ [1212 if African American origin] (SCr in μmol/L)
CKD-EPI [11]	♂; SCr ≤0.9	$GFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{age} \times$ [1.159 if African American origin] (SCr in mg/dL)
	♂; SCr >0.9	$GFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{age} \times$ [1.159 if African American origin] (SCr in mg/dL)
	♀; SCr ≤0.7	$GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{age} \times$ [1.159 if African American origin] (SCr in mg/dL)
	♀; SCr >0.7	$GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{age} \times$ [1.159 if African American origin] (SCr in mg/dL)
FAS equation [12]	Age ≤40 years	$GFR = 107.3/(SCr/Q)$ (SCr in mg/dL)
	Age >40 years	$GFR = 107.3/(SCr/Q) \times 0.988^{(age-40)}$ (SCr in mg/dL)
	♂ Q = 0.9, ♀ Q = 0.7	
RLM [13]		$GFR = e^{X - 0.0158 \times age + 0.438 \times \ln(age)}$
	♂; SCr <180	$X = 2.56 + 0.00968 \times (180 - SCr)$ (SCr in μmol/L)
	♂; SCr ≥180	$X = 2.56 - 0.926 \times \ln(SCr/180)$ (SCr in μmol/L)
	♀; SCr <150	$X = 2.50 + 0.0121 \times (150 - SCr)$ (SCr in μmol/L)
	♀; SCr ≥150	$X = 2.50 - 0.926 \times \ln(SCr/150)$ (SCr in μmol/L)

SCr, serum creatinine.

creatinine concentration was measured using a kinetic colorimetric compensated Jaffé technique (Roche Modular system) whose results were standardized against the concentrations obtained by liquid chromatography–mass spectrometry by linear regression adjustment. The calibration equation was as follows: standardized plasma creatinine = 0.9395 × Jaffé compensated serum creatinine (in μmol/L) + 4.6964. The coefficient of correlation was 0.97. After, all plasma creatinine values were obtained by an enzymatic technique. eGFR was calculated using the CKD-EPI, MDRD, FAS and RLM formulas as described in Table 1.

GFR categories and GFR evolution

GFR categories were defined as ≥90 mL/min/1.73 m^2 (Stage 1), <90–≥60 mL/min/1.73 m^2 (Stage 2), <60–≥45 mL/min/1.73 m^2 (Stage 3A), <45–≥30 mL/min/1.73 m^2 (Stage 3B), <30–≥15 mL/min/1.73 m^2 (Stage 4) and <15 mL/min/1.73 m^2 (Stage 5) [19]. The decline in renal function was assessed by absolute mGFR slope, defined as the regression coefficient between mGFR and time (in mL/min per 1.73 m^2/year), and relative mGFR slopes, estimated with linear mixed models with log-transformed GFRs. The parameter estimate can be interpreted as a relative slope expressed as the per cent (%) per year after the following transformation: [exp(estimate) − 1] × 100. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines suggest that eGFR normally declines by <1 mL/min/1.73 m^2/year from a level of 125 mL/min/1.73 m^2 once adulthood is reached [20]. Any reduction ≥1 mL/min/1.73 m^2/year, i.e. a slope more negative than or equal to −1 mL/min/1.73 m^2/year (≤−1), was considered a progressive disease, otherwise it was considered non-progressive [21–23]. We defined two groups of patients: those with a GFR slope reporting a loss ≥−1 mL/min/1.73 m^2/year were defined as patients with a rapid GFR decline and those with a GFR slope reporting a loss <−1 mL/min/1.73 m^2/year were defined as patients with a slow GFR decline. We also conducted an analysis where we removed the correction for BSA and assessed mGFR slopes in mL/min/year.

Performance of equations—statistics analysis

To assess the performance of equations, we conducted two analyses: a cross-sectional analysis and a longitudinal analysis. For the cross-sectional analysis we selected one mGFR per patient performed after 8 June 2009 where the enzymatic creatinine assay was settled.

For the longitudinal analysis, absolute and relative eGFR slopes were calculated as described above for each equation (MDRD, CKD-EPI, FAS and RLM).

The performances of the MDRD, CKD-EPI, FAS and RLM equations were compared for bias, precision, accuracy and correlation. Bias was defined as the mean difference between eGFR and mGFR. Precision was assessed by the 95% limits of agreement (LoA) of the eGFR:mGFR ratio, the Bland and Altman LoA between mGFR and eGFR and the standard deviation (SD) between eGFR and mGFR. The root mean square error (RMSE) of eGFR−mGFR differences was calculated to highlight imprecision. Accuracy was assessed by accuracy 30% (P30), which is the percentage of patients whose eGFR is within a 30% deviation of their mGFR. Comparisons of bias and accuracy (P30) were performed using the paired *t*-test and McNemar's test, respectively. For the longitudinal analysis, we categorized patients in three groups according to GFR evolution: 'stable' for those with a ±10% GFR variation, 'decliners' for those with a GFR decrease >10% and 'improvers' for those with a GFR increase >10%. We then conducted a κ analysis to evaluate classification according to each eGFR formula compared with mGFR. Data were analysed using GraphPad Prism version 6.0 (GraphPad Software, La Jolla, CA, USA) software. Data are expressed as frequency, mean ± SD or median and interquartile range (IQR) when variables were not normally distributed. Distributions were tested for normality using the D'Agostino–Pearson test. Simple comparisons were made using the Mann–Whitney U test. The chi-square test was used to compare categorical measures. P-values <0.05 were considered statistically significant in all analyses.

RESULTS

Patient characteristics

Patient characteristics are shown in Table 2. Forty patients (19 men) were included. The mean age was 45.4 ± 16.8 years, mean BMI was 19.8 ± 3.4 kg/m^2 and mean BSA was 1.60 ± 0.17 m^2 . Patients received HPN for 3.1 ± 3.9 years for a short bowel syndrome [75% (n = 30)] or a non-functional intestinal tract [25% (n = 10)]. The aetiologies for IF varied as

Table 2. Clinical and biological characteristics of patients with parenteral nutrition having either slow or rapid decline of mGFR

Characteristics	All population ($n = 40$)	Slow GFR decline <1 mL/min/1.73 m^2/year ($n = 17$)	Rapid GFR decline >1 mL/min/1.73 m^2/year ($n = 23$)	P-value
Clinical characteristics				
Men/women, *n*/*n*	21/19	6/11	15/8	0.20
Age (years)	45.4 ± 16.8	47.2 ± 16.8	44.1 ± 17.0	0.79
BMI (kg/m$^{2)}$	19.8 ± 3.4	19.6 ± 2.2	19.9 ± 4.2	0.92
Duration of HPN (years)	3.1 ± 3.9	3.2 ± 4.1	3.0 ± 3.9	0.88
History of renal lithiasis, *n* (%)	14 (35)	7 (41)	7 (30)	0.57
History of high blood pressure, *n* (%)	4 (10)	3 (18)	1 (4)	0.19
History of single kidney, *n* (%)	1 (2.5)	0	1 (4)	0.25
History of diabetes, *n* (%)	1 (2.5)	0	1 (4)	0.25
Aetiology of IF, *n* (%)				
Vascular infarction	12 (32)	4 (23)	8 (35)	0.52
Congenital disease	5 (13)	2 (13)	3 (13)	0.91
CIPO	5 (13)	3 (18)	2 (9)	0.66
Crohn's disease	3 (8)	1 (6)	2 (9)	0.43
Tumour resection	3 (8)	1 (6)	2 (9)	0.75
Volvulus	3 (8)	2 (13)	1 (4)	0.40
Villous atrophy	3 (8)	3 (18)	0	0.04
Digestive perforation	3 (8)	0	3 (13)	0.14
Radiation enteritis	2 (5)	1 (6)	1 (4)	0.83
Autoimmune enteropathy	1 (2.5)	0	1 (4)	0.25
Intestinal status				
Short bowel syndrome, *n* (%)	30 (75)	12 (71)	18 (78)	0.78
Remnant small bowel length (cm), median (IQR)	67 (40–80)	80 (50–80)	60 (30–80)	0.31
Right colon present, *n* (%)	16 (40)	6 (35)	10 (43)	0.69
Stomia, *n* (%)	17 (43)	8 (47)	9 (39)	0.70
Composition of parenteral nutrition bag				
Bags per week	4.8 ± 1.7	4.7 ± 1.8	4.9 ± 1.7	0.53
Volume per bag (mL)	2213 ± 609	2167 ± 649	2253 ± 587	0.55
Nitrogen per bag (g)	10.2 ± 2.4	10.0 ± 2.4	10.3 ± 2.5	0.70
Sodium per bag (mmol)	160 ± 90	158 ± 94	161 ± 88	0.94
Number of renal investigations				
2	8	3	5	0.78
2–5	15	5	10	0.47
>5	17	9	8	0.38
Duration of follow up (years)	7.2 ± 4.3	7.2 ± 3.4	7.2 ± 5.0	0.68
Results of renal investigations				
mGFR (mL/min/1.73 m^2)	78 ± 28	71 ± 24	83 ± 30	0.28
mGFR evolution (mL/min/1.73 m^2/year)	−1.9 ± 4.3	−0.9 ± 2.8	−4.1 ± 4.0	<0.001
Diuresis (mL)	1219 ± 624	1262 ± 514	1185 ± 710	0.55
Albuminuria/creatinuria (mg/mmol), median (IQR)	1.1 (0.4–2.5)	0.7 (0.9–1.9)	1.2 (0.4–5.5)	0.17
TR Na	98.89 ± 0.97	99.00 ± 0.91	98.80 ± 1.06	0.82
TR Cl	98.02 ± 1.73	98.27 ± 1.35	97.83 ± 1.96	0.58
Urinary Na:K ratio, median (IQR)	1.89 (0.78–3.83)	1.92 (1.04–3.45)	1.85 (0.65–4.33)	0.73
Urinary Na:K ratio <1, *n* (%)	14 (35)	3 (18)	11 (48)	0.11
Urinary osmolality (mOsm/L)	666 ± 187	605 ± 174	723 ± 185	0.10

Data are expressed as mean ± SD unless stated otherwise. Differences between groups were tested using Kruskal–Wallis or chi-squared tests as appropriate.
TR Na, tubular reabsorption of sodium; TR Cl, tubular reabsorption of chloride.

described in Table 2. The most common aetiologies were mesenteric ischaemia [32% ($n = 12$)] and congenital disease [8% ($n = 5$)], including congenital malformation and Hirschsprung disease, and chronic intestinal pseudo-obstruction (CIPO) [8% ($n = 5$)]. Seventeen patients had a stoma (43%) and 16 patients still had their right colon (40%). Four patients had a history of high blood pressure, one had type 2 diabetes and one had a congenital single kidney. Fourteen patients had a history of renal lithiasis (35%). At inclusion, patients were treated with a mean of 4.8 ± 1.7 bags per week. The bags had a mean volume of 2213 ± 609 mL and contained 10.2 ± 2.4 g nitrogen and 160 ± 90 mmol sodium.

GFR measurements

A total of 205 GFR measurements were collected; each patient had an average of 5.1 ± 3.0 measures during a mean follow-up of 7.2 ± 4.3 years. Eight patients had both GFR measurement methods. The mean mGFR at inclusion was 78 ± 28 mL/min/1.73 m^2. Fifteen patients had CKD Stage 2, four patients

CKD Stage 3A, two patients had CKD Stage 3B and two patients had CKD Stage 4. The mean diuresis was 1219 ± 624 mL/24 h. Microalbuminuria affected 23% of patients ($n = 9$) and only one patient had macroalbuminuria (48 mg/mmol) and was known for a history of type 2 diabetes. The mean tubular reabsorption of sodium and chloride were, respectively, 98.09 ± 0.97% and 98.02 ± 1.73%. The urinary Na:K ratio was inverted in 35% of patients ($n = 14$) in favour of dehydration at the time of the GFR measurement. The urinary osmolality was high at 666 ± 187 mOsm/L. A 24-h urinary collection was available for 30 of 40 patients and urinary creatinine clearance was 95 ± 34 mL/min.

GFR evolution and factors associated with kidney impairment

During the follow-up, the mean mGFR declined by 1.9 mL/min/1.73 m^2/year and the relative decline was 11.3%. Without BSA indexation the mGFR decline is −1.51 mL/min/year. Thirty-two patients had an mGFR decrease of −0.5 to −18 mL/min/1.73 m^2/year, two patients showed a stable mGFR during the follow-up and six patients had an mGFR increase from 1.5 to 9 mL/min/1.73 m^2/year. Twenty-one patients had a rapid kidney function decline (≥1 mL/min/1.73 m^2), with a mean mGFR decrease of 4.1 ± 4.0 mL/min/1.73 m^2/year, and 19 patients had a slow kidney function decline (<1 mL/min/1.73 m^2), with an mGFR decrease of 0.9 ± 2.8 mL/min/1.73 m^2/year. There was no significant association between age, BMI, history of lithiasis, albuminuria, duration or composition of HPN and decline of kidney function.

Initial mGFR was comparable in both groups (84 versus 74 mL/min/1.73 m^2, P = NS). In the rapid kidney function decline group, there was a non-significant trend where more patients exhibited an inverted urinary ratio: 48% ($n = 11$) versus 18% ($n = 3$), P = 0.11.

Performance of the formulas eGFR

The characteristics of patients during the mGFR used to evaluate the different kidney function equations are summarized in Supplementary data, Table S1. Cross-sectional performances of the formulas are described in Table 3 and Figure 1. All formulas overestimate mGFR in this population: the mean biases for the MDRD, CKD-EPI and FAS equations are high: 25.90, 21.40 and 24.70, respectively. The mean bias of the RLM equation was 13.03, which is significantly lower (P < 0.05) than that of the three other equations. Figure 1A shows these results; the gap between the regression line to the diagonal indicates a large bias. The MDRD, CKD-EPI and FAS equations are less accurate than the RLM equation: P30 is 45%, 50% and 50% versus 68%, respectively (Table 3). The precision was low in all equations with large 95% LoAs and SDs. The LoAs of the Bland and Altman plot were dispersed (Figure 1B).

Urinary creatinine clearance showed poor performance in estimating GFR (Supplementary data, Table S2): the mean bias is high (30.67), accuracy is low (P30 is 30%) and imprecision is high (RMSE is 957; Supplementary data, Table S3).

In the longitudinal analysis, all eGFR equations failed eGFR evolution: we observed a systematic underestimation of GFR slope and all evaluation parameters showed poor results (Table 4). Bias was smaller, prediction accuracy higher and 95% LoAs narrower for the CKD-EPI equation than for the MDRD and RLM equations, for both absolute and relative slopes. As compared with the CKD-EPI equation, the FAS equation had higher bias but a slightly better prediction accuracy for relative slopes. The κ analysis showed a fair agreement for every formula except for the RLM formula, in which agreement was only slight (Supplementary data, Table S3).

DISCUSSION

This study has demonstrated that during a median follow-up of 7.1 years and using a gold standard method, IF requiring HPN is associated with a marked decrease in kidney function without clear predisposing factors. We also showed that all eGFR formulas are inadequate in this population.

Kidney disease is common in patients with IF on HPN. In this cohort we found that 47% of patients had an mGFR <90 mL/min/1.73 m^2 and 20% <60 mL/min/1.73 m^2. These data are in agreement with previous studies that investigated mGFR in HPN patients. Boncompain-Gérard *et al.* [7] and Lauverjat *et al.* [6] described a decreased mGFR in almost 50% of patients in their cohort (respectively, 56% and 52%). In paediatric-onset IF, Moukarzel *et al.* [24] included 13 children on HPN, where all patients had impaired renal function (mean mGFR 65.5 mL/min/1.73 m^2). The decline of renal function has already been assessed by eGFR in two studies in adult populations: Buchman *et al.* [4] described a decline of 3.5% per year in 1993 and Pironi *et al.* [9] reported a decline of 2.8% per year. Here we present the first study reporting the GFR decline by a true mGFR. The decline was 1.9 mL/min/1.73 m^2, or 2.1% per year, which is slightly lower than what was previously described.

The pathophysiology of CKD in patients on HPN remains unclear. The subgroup analysis failed to reveal risk factors, as we did not find any significant association between decline in kidney function and demographic or clinical patients' characteristics, aetiology of IF or duration or composition of HPN (including volume of perfusion, amount of amino acids or sodium). In a cohort of 33 patients, Pironi *et al.* [9] did not find significant associations between the decline of renal function and the same criteria. We observed a tendency of an inverted negative urinary Na:K ratio in patients with faster kidney impairment, which would favour hypovolaemia. Because of the small sample of patients studied, there is a lack of power to show a significant difference. A previous study suspected that chronic dehydration could be responsible for kidney impairment since authors described an association between an inverted urinary Na:K ratio secondary to hyperaldosteronism and impaired kidney function [6]. In the paediatric population, the duration of HPN seemed to be correlated with renal impairment [5, 24], similar to a study carried out in adult patients by Buchman *et al.* [4]. In one study, an association between age and a decrease in GFR was found [4]. A short portion of the remaining small bowel was also associated with kidney failure in young patients [5]. In older patients, neither we nor others [4, 6] could confirm this association. Nephrotoxic medications, the number of episodes of bacteraemia or fungaemia, infection rate and the amount of amino acids have been associated with renal dysfunction in only one study [4] and not confirmed by others [9, 24]. Unfortunately, in our cohort, we did not collect a history of sepsis or medication that could have impacted renal function.

Most teams caring for HPN patients performed kidney function monitoring through the use of MDRD or CKD-EPI formulas. In a recent study performed by Van Rijn *et al.* [25] analysing data from 1955 patients, creatinine-based equations (CKD-EPI and MDRD) showed good performances to estimate GFR changes over time, but the extrapolation of these results to a specific population is uncertain.

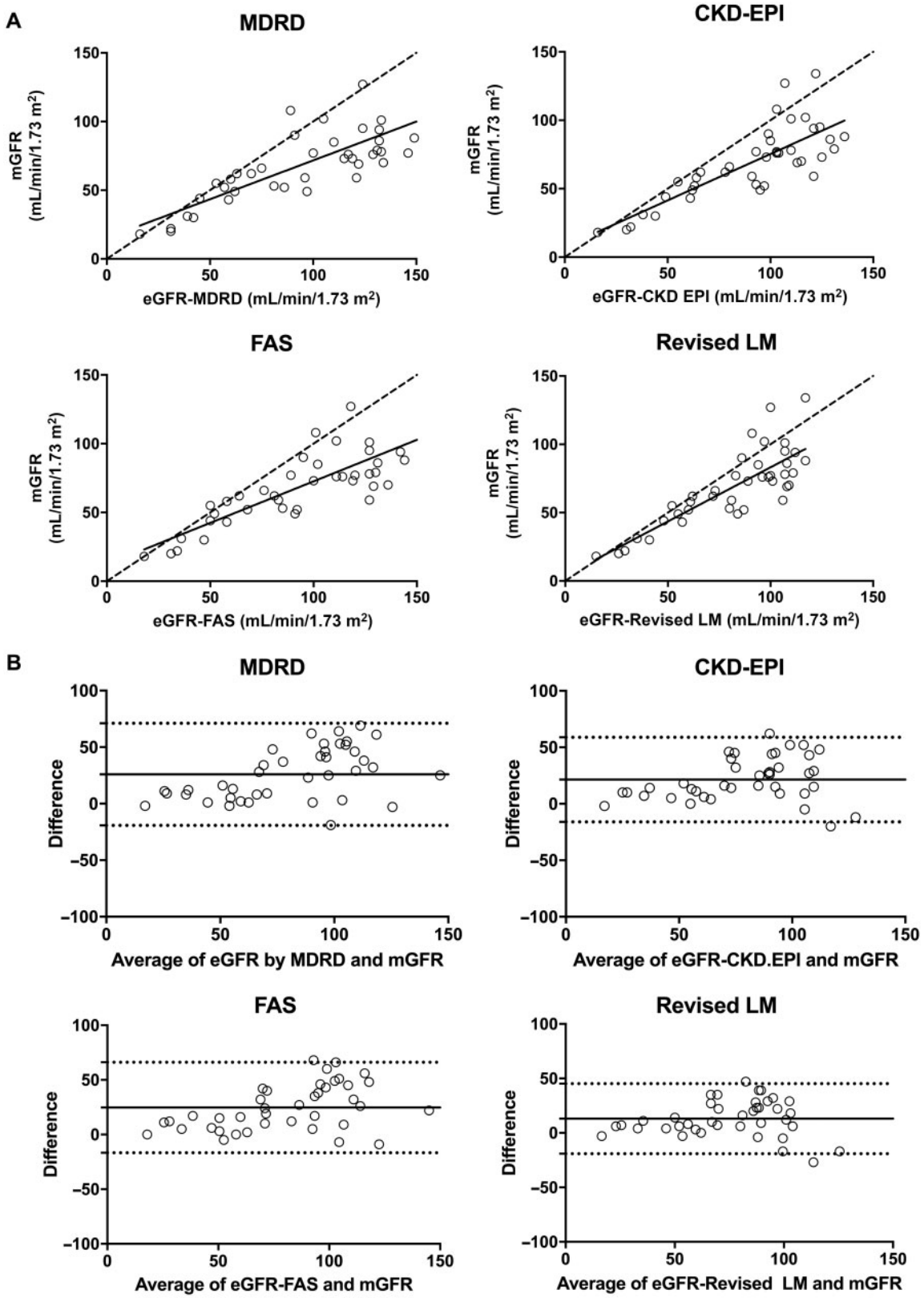

FIGURE 1: Performances of the MDRD, CKD-EPI, FAS and RLM equations. (A) Correlation diagram for the MDRD, CKD-EPI, FAS and RLM equations. The dashed line represents the perfect concordance and the continuous line the regression of mGFR on eGFR. (B) Bland and Altman plot for the MDRD, CKD-EPI, FAS and RLM equations. The continuous line represents the bias and the dotted lines represent the upper and lower limits of agreement.

Table 3. Performances of the CKD-EPI, MDRD, FAS and RLM equations

Equation	Bias	Bias 95% LoA	SD	RMSE	P30 (%)
MDRD	25.90*	−19.27; 71.07	23.05	694	45**
CKD-EPI	21.40*	−16.06; 58.86	19.11	477	50**
FAS	24.70*	−16.72; 66.12	21.13	631	45**
RLM	13.03	−19.13; 45.18	16.40	186	67.5

*$P < 0.001$ comparison of the RLM equation; **$P < 0.05$ comparison of the RLM equation.

Table 4. Mean GFR slopes and overall performance of estimating equations

Absolute slope (mL/min/1.73 m^2/ year)	Mean	Bias	95% LoA	SD	RMSE	P30 (%)
mGFR	−1.9 ± 4.3					
MDRD	−0.8 ± 6.4	1.2	−10.1; 12.4	5.8	7.1	10
CKD-EPI	−1.3 ± 4.8	0.6	−7.6; 8.9	4.2	4.6	22.5
FAS	−1.0 ± 5.6	0.9	−9.4; 11.3	5.3	6.2	12.5
RLM	−0.7 ± 4.1	1.3	−7.1; 9.7	4.3	5.9	17.5
Relative slope (%/year)						
mGFR	−11.3 ± 34.3					
MDRD	0.6 ± 48.4	12.0	−47.9; 71.8	30.5	173	27.5
CKD-EPI	−6.5 ± 34.4	4.8	−30.2; 39.9	17.9	41	30
FAS	−4.41 ± 37.4	6.9	−37.6; 51.5	22.7	71	32.5
RLM	−4.22 ± 37.1	7.1	−30.6; 44.8	19.2	70	25

Studies thus far have assessed the validity of creatinine-based GFR-predicting equations, specifically searching for the most reliable equation in HPN patients. Consequently, there is no reliable recommendation for estimating renal function in these patients. This is surprising, because patients on HPN have a higher prevalence of sarcopenia [26] and frequently have many factors that affect muscle mass and creatinine generation and thus kidney function estimation [27].

In this study we demonstrated that creatinine-based equations are inadequate for both transversal assessments of renal function and for longitudinal monitoring. All formulas largely overestimated renal function in a transversal assessment and underestimated the slope of GFR in a longitudinal analysis. The RLM equation significantly outperformed all the other equations in the transversal assessment but showed poor results to predict GFR changes over time. In our population, the MDRD, CKD-EPI, FAS and RLM equations failed to reliably estimate GFR with good performance, which leads us to advise against the use of these equations.

Creatinine-based equations are useless in this population because of the high prevalence of sarcopenia: in our cohort, mean 24-h creatininuria was low (7.9 ± 3.4 mmol/24 h) compared with patients with similar renal function [28]. The second issue generated by these formulas is systematic BSA indexation. While it may have a limited impact on patients of 'normal' body size, it will have a strong impact in a lean population. In this cohort, the mean BMI was 19.8 ± 3.4 kg/m^2 and the mean BSA was 1.60 ± 0.17 m^2: BSA indexation in our population tends to overestimate both GFR values (7 mL/min/1.73 m^2) and GFR slope. These results are inconsistent with an article written by Delanaye *et al.* [29] reporting an overestimation of 14 mL/min after indexation in patients with a BMI <18 kg/m^2. Thus we recommend that mGFR should be prioritized over eGFR where possible.

Our study has some limitations. First, the design is retrospective. However, previous studies analysing renal impairment were all retrospective, from data collected during the routine follow-up [4, 9], or were cross-sectional [5–7, 24]. Second, the number of patients is limited. The lack of evidence of risk factors for impaired renal function may be related to the small number of patients. However, this cohort is the largest, except one that included patients with intestinal transplantation [9]. Third, the definition of low or rapid decliner (>1 or <1 mL/min/1.73 m^2) is critical. The population was too small to use another cut-off. But it should be noted that the κ analysis with three groups gave similar results.

In conclusion, the risk of developing kidney disease in this population seems important. Monitoring kidney function with a gold standard method is recommended. Based on these results, it would be interesting in future studies to prospectively follow other clinical and biological data such as blood pressure, excretion fraction of urea and sodium and uricaemia.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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AUTHORS' CONTRIBUTIONS

The research idea and study design were carried out by L.K., M.L. and C.C. Recruitment and follow-up of patients were

done by M.L., D.B. and C.C. Data acquisition was done by E.C. Data analysis and interpretation were carried out by E.C., L.K. and D.F. Statistical analysis was done by E.C. and L.K. L.K. is the guarantor of this work and, as such, takes full responsibility for its content.

CONFLICT OF INTEREST STATEMENT

None declared.

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