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Original Article

Relationship between gastric emptying and clinical and biochemical factors in chronic haemodialysis patients

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Abstract

Background. Gastroparesis is an important side-effect of end-stage renal disease because of its influence on nutritional status.

Methods. In this study, 56 equilibrated haemodialysis patients were evaluated by radioisotopic examination for gastric emptying time. These data were correlated to anthropometrical as well as biochemical parameters.

Results. The half-life time for gastric emptying was 83 ± 34 min in the overall population, compared to 50 ± 15 min in a normal reference population. Prealbumin, mean fibular nerve-conduction velocity and intra- as well as extracorpuscular folic acid were significantly different between patients with the lowest and highest gastric emptying times. Linear correlation analysis between the half-life for residual radioactivity and the remaining parameters yielded a significant correlation for blood urea nitrogen, serum folic acid, intracorpuscular folic acid, serum vitamin B_{12}, serum C-reactive protein, serum prealbumin and mean fibular nerve-conduction velocity.

Conclusions. This study demonstrates that gastric emptying is significantly delayed in end-stage renal disease patients. The delay is associated with changes in biochemical indicators of nutritional status such as serum albumin and prealbumin.

Keywords: end-stage renal disease; gastroparesis; nerve conduction velocity; nutritional status; vitamin B_{12}

Introduction

Malnutrition remains a major problem in end-stage renal disease (ESRD) with a reported incidence from 13 to 20% [1,2]. This malnutrition has an important impact on morbidity and even mortality, by affecting immune function [3] and cardiovascular stability [4]. Therefore, attempts should be made to correct all conditions with a possibly negative impact on the nutritional status such as chronic inflammation, cardiac failure, disturbances of hepatic function, retention of uraemic toxins and functional alterations of the gastrointestinal (GI) tract.

Experience with other conditions complicated by malnutrition, such as diabetes mellitus [5], critical illness [6], and hepatic cirrhosis [7] suggest that alterations in gastric emptying might play a crucial role. In addition, gastric emptying is at least in part dependent on nerve function [8], which is known to be disturbed in renal failure.

The issue of gastric emptying in ESRD has been considered in a limited number of studies, each with substantial shortcomings. One study was conducted on rats [9], another in children [10], while some investigated exclusively Asian patients [11,12], allowing no direct extrapolation of the results to an adult Caucasian population. In addition, many studies were based on a limited number of subjects [10,13–20] and did not allow definitive conclusions. Different methods for measuring gastric emptying time were used, ranging from radio-isotopic investigation to echography and electrogastrography. Hence, results obtained and cut-off values were not always comparable.

In the present study, gastric emptying was evaluated in 56 haemodialysis patients and compared with that of a healthy control group. The obtained results are correlated to a set of anthropometric, clinical, and biochemical patient characteristics.

Subjects and methods

The trial was conducted in accordance with the current version of the Declaration of Helsinki, and was undertaken after full approval by the local ethical committee. Patients were entered after giving informed consent. The study was limited to one single hospital, to avoid differences

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in evaluation protocol of gastric emptying and in therapeutic approach of renal failure. For the same reason CAPD patients were not entered in the study; conceivably their intestinal motility as well as the registration of radioactive signals over the abdomen might be different from haemodialysis patients, due to the presence of the dialysis solution in the peritoneal cavity.

Patient recruitment

Patients, older than 18 years, on a regular haemodialysis schedule for at least 3 months before their enrolment, who had given signed or oral witnessed informed consent before the start of the trial were included. Excluded were patients with mechanical obstruction of the GI tract and with known GI cancer or active ulcer disease. Patients who could become pregnant during the study period (i.e. not being postmenopausal or not using adequate contraceptive measures), with alcoholism (defined as a daily intake of >4 units of alcohol), who started with parenteral hyperalimentation within 4 weeks before the study, who were unable to adequately express their subjective complaints or with a history of major GI surgery (except for appendectomy, cholecystectomy and herniotomy) were also excluded. Medications that could influence GI motility and function (e.g. dopamine agonists, tricyclic antidepressants, anticholinergics, H2 antagonists, proton-pump blockers, prokinetics, spasmolytics, opiates, and macrolide antibiotics) were discontinued at least 2 weeks prior to the study start. Applied to the patient population of the dialysis centre in the University Hospital of Gent, these criteria resulted in the selection of 56 patients who were submitted to an initial screening.

Haemodialysis characteristics

All patients were dialysed three times weekly for 3–4 h with bicarbonate as a dialysate buffer and with non-complement-activating membranes. The composition of the dialysate was Na^+ 137 mEq/l, K^+ 1–2 mEq/l, Cl^- 97 mEq/l, CH_3COO^- 5 mEq/l and HCO_3^- 36 mEq/l. Blood flows and dialysate flows of >250 ml/min and 500 ml/min were pursued. Adequacy of dialysis was evaluated by monthly controls of the ratio of total urea clearance over its distribution volume (Kt/V), using a single-pool kinetic model (post-dialysis blood sample collected 15 min after the end of the dialysis session). The target value per session was 1.3.

Vitamin B complex was administered monthly by routine intravenous injection in the bubble trap chamber (thiamine, pyridoxine, and cyanocobalamin—Neurobion®, Merck-Belgolabo NV, Overijse, Belgium) in a dose of 1 ampoule monthly at the end of a dialysis session. In patients with prominent motor and sensory nerve conduction disturbances and/or low serum levels of vitamin B_{12}, the frequency of administration was increased to once weekly.

Vitamin D supplementation was titrated according to serum PTH levels whereby a threshold serum PTH concentration of 100–200 pg/ml was implemented for the initiation of the therapy. If PTH levels rose above this level, alfacalcidol (One-alpha Leo®, Leo Pharmaceutical Products Trading Ltd, Ballerup, Denmark) was orally administered in three weekly pulsed doses (0.5–4.0 mg/pulse). Serum PTH and $1,25(OH)_2$ vitamin D3 levels were checked bi-monthly and alfacalcidol doses were adjusted accordingly.

Haematocrit levels were determined every 2 weeks and target values of 32–35% were pursued. If the observed value was lower, recombinant human erythropoietin was administered three times weekly at the end of each dialysis session. Both intravenous (Recormon®, Boehringer–Mannheim GmbH, Mannheim, Germany or Eprex®, Janssen–Cilag, Schaffhausen, Switzerland) as well as subcutaneous administrations (Recormon®, Boehringer) were applied.

Serum ferritin was targeted at 200 ng/ml and transferrin saturation at 20% or more. If these conditions were not met, intravenous iron supplements (Venofer®, Vifor Inc., St Gallen, Switzerland) were administered weekly.

Test procedure and data analysis

Trans-sectional analysis. A determination of gastric emptying was performed in all patients ($n=56$). For this measurement a radioisotopic evaluation was used, whereby a standardized solid meal of ± 260 g (one scrambled egg, well done and labelled with 500 mCi of Technetium-99m-sulphur colloid, two slices of white bread (± 50 g each), and 150 ml of water), with a caloric content of 231 kcal (47% carbohydrate, 18% protein, 35% fat) was presented to each patient. The test was performed on a dialysis-free day, and patients were instructed to fast overnight. Smoking was not allowed during 12 h preceding the test. The total meal consumption time was limited to 10 min, and the moment at which the meal had been ingested completely was labelled as time 0. After ingestion of the meal, anterior and posterior images were acquired with the patient in sitting position using a double-headed gamma camera equipped with a low-energy high-resolution collimator and interfaced to a nuclear medicine computer system. Twenty-per cent energy windows were set with peaks at 140 keV. The anterior and posterior images were acquired for 1 min in both energy windows at 0, 10, and 20 min and from then every 20 min. Patients remained seated between acquisitions. If 50% of the meal had not been emptied from the stomach after 120 min, acquisition was continued until 50% of the meal had emptied. Data was stored on an on-line computer.

The gastric counts were determined for each image in the marked region of interest, and corrected for background, scatter, and radioactive decay. Values for relative residual radioactivity (RAA) for the solid component of the meal, using the activity at time 0 as 100%, were calculated at each time point. Results were then presented graphically and curve-fitting was applied in order to determine the values for the time by which half of the gastric content had been evacuated ($T_{\frac{1}{2}}$) and the area under the curve ($AUC_{0-120\ min}$) of the RAA *vs* time plot. The normal value $\pm$ standard deviation of $T_{\frac{1}{2}}$ obtained for a solid meal in healthy subjects, using the above procedures, by a Working Party of the Belgian Association for Nuclear Medicine, of which the unit where the examinations were performed is a member, was 50 ± 15 min (i.e. $T_{\frac{1}{2}} + 2\ SD = 80$).

Patient characteristics and biochemical parameters. Additionally, anthropometric as well as biochemical data were collected for each patient at the time of the gastric emptying test. The following patient characteristics were registered: gender, age, time since start of haemodialysis, and the primary renal diagnosis. As biochemical data, serum haemoglobin (Hgb), ferritin, transferrin, Na^+, K^+, Ca^{2+} corrected for plasma protein, $P3^-$, Mg^{2+}, predialysis blood urea nitrogen (BUN), serum creatinine, red blood cell count (RBC), white blood cell count (WBC), serum

albumin, arterial pH, intact parathyroid hormone (iPTH), intracellular and extracellular folic acid, vitamin B_{12}, $1,25(OH)_2$ vitamin D3, cholesterol (CH), red-cell sedimentation rate (ESR), serum C-reactive protein (CRP), prealbumin, residual creatinine clearance, protein catabolic rate (PCR), and Kt/V were included.

Aluminium accumulation was evaluated by performing a desferrioxamine test. Desferrioxamine (Desferal®, Ciba–Geigy, Basel, Switzerland) 1500 mg was administered intravenously through the arteriovenous fistula or central venous access catheter during the last 30 min of the haemodialysis session. Serum aluminium levels were measured immediately before and 44 h after the desferrioxamine administration.

Finally, mean conductive velocity in the fibular nerve, as measured by needle electromyography, was also submitted to analysis.

Statistical analysis. After comparison with the control group, the entire ESRD population was divided into three equal groups based on the value obtained from the gastric emptying test. The two outermost groups (i.e. those with the highest and lowest values) were then compared for all anthropometric and biochemical parameters.

In addition, a linear regression analysis was performed for all patients, between the $T\frac{1}{2}$ and the anthropometric and biochemical parameters. Parameters rendering a P value $\leqslant 0.05$ were grouped and further submitted to a stepwise multifactorial regression.

The same test procedure was repeated with the area under the curve (AUC) as dependent variable.

Statistical methods

Data are given as mean $\pm$ standard deviation. To compare different groups intermutually, analyses were performed by the ANOVA, the Fisher exact, the Wilcoxon signed rank and the Mann–Whitney U-test where appropriate. Significance was accepted for $P \leqslant 0.05$. Linear correlation analysis was performed using the GraphPad Prism™ statistical package version 1.00, GraphPad® Software. In addition, a stepwise multifactorial regression was executed using the Unistat® Statistical Package version 3.0a, Unistat© Ltd 1984–1995.

Results

The overall group of 56 patients consisted of 22 males and 34 females. The average age was 65.5 ± 13.5 years and the patients had been on haemodialysis for 3.5 ± 4.5 years. Their primary renal diagnosis was hereditary nephropathy ($n = 5$), chronic interstitial nephritis ($n = 30$), diabetic nephropathy ($n = 12$), IgA nephropathy ($n = 3$) and other forms of chronic glomerulonephritis ($n = 6$). The residual creatinine clearance in the non-anuric patients was 2.9 ± 4.7 ml/min. Thirty-seven patients were anuric. Kt/V values of 1.3 ± 0.2 were achieved.

After division of the entire population into three groups according to their gastric emptying (as measured by $T\frac{1}{2}$ for RAA and AUC), no significant differences could be observed in gender, age, and time on dialysis (Table 1). The primary diagnosis was not significantly different between groups.

Comparison (Table 2) of the groups with the shortest half-life ($T\frac{1}{2} = 45 \pm 10$ min) and the longest half-life for RAA (122 ± 14 min), demonstrated that prealbumin was higher ($P = 0.02$) and that the mean fibular nerve conduction velocity was faster ($P = 0.05$) in patients with the shorter gastric emptying. Furthermore, a higher folic acid concentration in serum ($P = 0.03$) as well as in the red blood cells ($P < 0.01$) was found for the group with the shorter gastric emptying. The borderline of significance was reached for BUN ($P = 0.07$) and erythrocyte sedimentation rate ($P = 0.09$). Other parameters were not significantly different, although there was a trend for CRP to be higher in the group with high-range $T\frac{1}{2}$.

Linear correlation analysis between the $T\frac{1}{2}$ for the RAA and the remaining parameters, yielded significant correlations (Table 3) for BUN, serum folic acid, intracorpuscular folic acid, serum vitamin B_{12}, serum CRP, serum prealbumin, and mean fibular nerve conduction velocity. A similar analysis with the AUC as the fixed correlation factor demonstrated significant correlations for BUN, serum folic acid, intracorpuscular folic acid, serum vitamin B_{12}, prealbumin, mean fibular nerve conduction velocity, aluminium 44 h after administration of desferrioxamine and CRP.

Parameters rendering a P value < 0.10 in the linear correlation analysis were entered in a stepwise regression analysis with the $T\frac{1}{2}$ of RAA taken as the dependent variable. Parameters included were: aluminium 44 h after administration of desferrioxamine, CRP, prealbumin, intracorpuscular folic acid, vitamin B_{12}, BUN, albumin fraction of total protein, and mean fibular nerve conduction velocity. Serum folic acid was omitted because of the clear interrelationship between this value and the intracorpuscular folic acid level. After completion of the regression analysis, only serum prealbumin ($P = 0.0009$), intracorpuscular folic acid

Table 1. Patient characteristics of the three groups divided according to their $T\frac{1}{2}$ RAA

	Low $T\frac{1}{2}$ RAA	Mid $T\frac{1}{2}$ RAA	High $T\frac{1}{2}$ RAA	Overall $T\frac{1}{2}$ RAA
Gender (m/f)	8/11	8/10	6/13	22/34
Age (years)	64.9 ± 12.8	66.2 ± 13.7	65.7 ± 14.3	65.6 ± 13.9
Time on dialysis (years)	2.1 ± 2.8	5.1 ± 4.7	3.5 ± 5.3	3.8 ± 5.8
$T\frac{1}{2}$ RAA (min)	45 ± 10	83 ± 11	122 ± 14	83 ± 34

$T\frac{1}{2}$ RAA, half-life time for gastric emptying; the normal value $\pm$ standard deviation of $T\frac{1}{2}$ obtained for a solid meal in healthy subjects, using the above procedures, by the Working Party of the Belgian Association for Nuclear Medicine, of which the unit where the examinations were performed is a member, was 50 ± 15 min (i.e. $T\frac{1}{2} + 2$ SD = 80).

Table 2. Parameters in the two-group analysis

	Low-range half-life for RAA	High-range half-life for RAA	*P*
$T_{\frac{1}{2}}$ (min)	**45 ± 10**	**122 ± 14**	**< 0.0001**
Age (years)	64.5 ± 13	66.1 ± 14.6	1.00
Na (mEq/l)	136 ± 3	137 ± 3	0.3056
BUN (g/l)	10 ± 0.33	7.9 ± 0.21	0.0674
S_{Crea} (mg/100 ml)	9.22 ± 3.21	9.39 ± 1.95	0.8276
K (mEq/l)	5.4 ± 0.6	5.3 ± 0.8	0.472
iCa (mEq/l)	10.29 ± 1.42	10.5 ± 0.87	0.215
P (mEq/l)	5.8 ± 1.5	5.9 ± 2.9	0.7939
Mg (mEq/l)	2.7 ± 0.7	2.8 ± 0.4	0.2396
Ferritin (ng/ml)	249 ± 131	255 ± 194	1.00
Transferrin (g/l)	2.07 ± 0.58	1.92 ± 0.33	0.331
CH (mg/dl)	203 ± 57	207 ± 57	0.663
FA (e) (g/l)	**8.25 ± 3.5**	**6.18 ± 0.9**	**0.0299**
FA (i) (g/l)	**519 ± 130**	**386 ± 135**	**0.0083**
Vit B_{12} (ng/l)	1373.2 ± 529.4	1700 ± 461	0.222
$1,25(OH)_2D3$ (pg/ml)	28.81 ± 13.54	20.78 ± 7.53	0.758
iPTH (pg/ml)	218.8 ± 259.6	282 ± 320.5	0.76
RBC ($10^6/mm^3$)	3.61 ± 0.35	3.5 ± 0.36	0.4459
WBC ($1000/mm^3$)	7.86 ± 1.72	7.16 ± 1.97	0.4591
Hb (g/dl)	11.19 ± 1.24	11.15 ± 1.4	0.9306
pH	7.34 ± 0.05	7.33 ± 0.05	0.7557
Albumin (g/l)	3.81 ± 0.27	3.7 ± 0.48	0.3379
ESR 1 h (mm)	38 ± 22	51 ± 28	0.0934
ESR 2 h (mm)	66 ± 30	75 ± 29	0.0853
CRP (mg/dl)	0.92 ± 1.08	2.4 ± 3.26	0.1274
Prealbumin (g/l)	**0.33 ± 0.08**	**0.28 ± 0.05**	**0.0174**
Residual Cl (ml/min)	2.06 ± 4.86	0.5 ± 1.26	0.1305
PCR	1.04 ± 0.32	0.94 ± 0.27	0.2663
Kt/V	1.23 ± 0.25	1.29 ± 0.12	0.5135
Time on dialysis (years)	2.18 ± 2.86	3.57 ± 5.48	0.6319
Mean N. Fib v (m/s)	**40.32 ± 6.34**	**34.45 ± 6.17**	**0.0528**
Desferrioxamine −1 h (mEq/l)	14.11 ± 12.7	18.88 ± 17.4	0.37
Desferrioxamine 44 h (mEq/l)	34.17 ± 16.7	56.59 ± 39.8	0.24
AUC RAA × min	6096 ± 1193	8834 ± 768	0.19

Significance between groups is indicated in bold ($P \leqslant 0.05$). Low-range half-life, patients with the lower half-life time for RAA; High-range half-life, patients with the higher half-life time for RAA. $T_{\frac{1}{2}}$, half-life time for gastric emptying; RAA, residual radioactive activity; Age, subject age; Na, serum sodium; BUN, predialysis blood urea nitrogen; S_{Crea}, serum creatinine; K, serum potassium; iCa, ionized serum calcium; P, serum phosphorus; Mg, serum magnesium; Ferritin, serum ferritin; Transferrin, serum transferrin; CH, serum cholesterol; FA (e), extracorpuscular folic acid; FA (i), intracorpuscular folic acid; Vit B_{12}, serum vitamin B_{12}; $1,25(OH)_2D3$, serum 1,25 dihydroxy vitamin D3; iPTH, intact parathyroid hormone; RBC, peripheral red blood cell count; WBC, peripheral white blood cell count; Hb, blood haemoglobin concentration; pH, blood pH; Albumin, serum albumin; ESR 1 h, erythrocyte sedimentation rate after 1 h; ESR 2 h, erythrocyte sedimentation rate after 2 h; CRP, serum C-reactive protein; Prealbumin, serum prealbumin; Residual Cl, residual creatinine clearance; PCR, protein catabolic rate; Kt/V, clearance of urea over its distribution volume; Mean N. Fib v, mean conduction velocity in the fibular nerve; Desferrioxamine −1 h, serum aluminium 1 h before desferrioxamine administration; Desferrioxamine 44 h, serum aluminium 44 h after desferrioxamine administration; AUC, area under the curve for residual radioactive activity.

($P = 0.0006$), and vitamin B_{12} ($P = 0.0006$) were entered into the equation. In a similar procedure for the AUC, the following parameters were included: pO_2, aluminium 44 h after administration of desferrioxamine, CRP, prealbumin, corpuscular folic acid, vitamin B_{12}, urea, TIBC, albumin fraction of total protein, and mean fibular nerve conduction velocity. In this case, serum prealbumin ($P = 0.0089$) and aluminium 44 h after administration of desferrioxamine ($P = 0.0182$) proved to be of significant importance.

Discussion

This study was undertaken to evaluate the pathophysiological importance of changes in gastric emptying in haemodialysed ESRD patients. The most important conclusion is that gastric emptying is dramatically disturbed in a substantial fraction of this haemodialysis population, despite adequate dialysis according to currently accepted standards.

Although the issue of gastric emptying has frequently been studied in other conditions, studies in adults suffering from uraemia are scant and of limited size [10,13–22]. In the present study, comparing 56 haemodialysed patients with a control group, it is clear that a substantial number of these patients suffer from severe gastric emptying disturbances. In 20 patients, gastric emptying time is at least doubled compared to the normal value of $T_{\frac{1}{2}}$ as defined by a Working Party of the Belgian Association for Nuclear Medicine. These alterations occurred in spite

Table 3. Linear correlation coefficients of the presented parameters *vs* the $T_{\frac{1}{2}}$ for RAA and the area under curve (AUC)

Parameter	r $T_{\frac{1}{2}}$	r AUC	Parameter	r $T_{\frac{1}{2}}$	r AUC
Age	+0.06	+0.03	RBC	−0.05	−0.07
Na	+0.13	+0.11	WBC	−0.17	−0.19
BUN*^{o}	−0.31	−0.35	Hb	−0.01	−0.02
S_{Crea}	−0.06	−0.06	pH	−0.09	−0.11
K	−0.06	−0.19	Albumin	−0.18	−0.11
iCa	+0.06	+0.05	ESR 1 h	+0.21	+0.23
P	+0.02	+0.05	ESR 2 h	+0.21	+0.22
Mg	+0.03	+0.05	CRP*^{o}	+0.34	+0.32
Ferritin	+0.05	+0.04	Prealbumin*^{o}	−0.38	−0.40
Transferrin	−0.19	−0.14	Residual CI	−0.19	−0.20
CH	+0.03	+0.04	PCR	−0.18	−0.19
FA (e)*^{o}	−0.29	−0.26	Kt/V	+0.13	+0.21
FA (i)*^{o}	−0.35	−0.32	Time on dialysis	+0.10	+0.17
Vitamin B_{12}^{*o}	+0.31	+0.30	Mean fibular nerve v*^{o}	−0.36	−0.33
$1,25(OH)_2D3$	−0.15	−0.13	Desferioxamine −1 h	+0.13	+0.13
iPTH	+0.03	+0.08	Desferioxamine 44 h^{o}	+0.29	+0.38

Significant ($P \leqslant 0.05$) correlations with $T_{\frac{1}{2}}$ are indicated by * and with AUC are indicated by ^{o}. Abbreviations as in Table 2.

of haemodialysis conforming to the current standards of adequate treatment (Kt/V $\geqslant 1.3$, dialysis time $\geqslant 3 \times 4$ h a week, with non-complement-activating dialysers and bicarbonate dialysate).

The gastric emptying data obtained in the present study were correlated with various parameters (Table 3). A significant correlation was found with some parameters of nutritional status and of nerve conduction. Regarding nutritional status, gastric emptying was significantly correlated with serum prealbumin and to a lesser extent also to serum albumin. Both parameters are considered to be indices of nutritional status [3]. Also the correlation with blood urea should be considered in the same context: a direct positive relationship was found, meaning that urea was higher in patients with the better gastric emptying times. Urea concentrations both depend on dialysis adequacy and protein intake. In this regard, it is of note that, except for extremely high values, an inverse relationship between urea and survival on dialysis has been observed, indicating that a high urea in this context should rather be considered as a beneficial index related to adequate nutrition than to a negative indicator related to inadequate dialysis [23]. All these data together suggest that adequate gastric emptying in dialysis patients leads to a better nutritional status.

Another group of parameters to which gastric emptying seems to be linked is nerve conduction. A direct correlation is found with fibular nerve motor velocity. Although intestinal motility is predominantly dependent on the splanchnic nerve system, it can be assumed that motor nerve function correlates well with autonomic nerve function in ESRD. Evaluation of the autonomic nervous system, by performing a power spectral analysis of the blood pressure and heart frequency could even result in stronger correlation and might be an even more appropriate study method in this regard; this should be considered for further evaluation.

The peculiar negative correlation with vitamin B_{12} can be explained by the fact that patients with the most compromised nerve function, and consequently the slowest gastric emptying, receive the highest doses of vitamin B_{12} [24,25]. In contrast, it is reported in at least one publication that vitamin B_{12} itself can be nocuous to nerve function [24]. In that way, our data might offer suggestion for a more careful administration of vitamin B_{12} in patient populations with motor nerve dysfunction. It is of interest to note that the vitamin B preparations that our patients receive on a regular basis do not contain folic acid. A positive correlation was found between folic acid and gastric emptying. Therefore the possibility should be considered that folic acid deficiency is somehow involved in the process of gastric dysmotility. No direct data are available to confirm this hypothesis. It has, however, been demonstrated that folic acid is involved in nervous function [25].

In conclusion, this study demonstrates that gastric emptying is significantly delayed in ESRD, affecting biochemical parameters of nutritional status and thus presumably leading to malnutrition.

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