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GASTRIC DYSFUNCTION IN DIALYSED PATIENTS WITH CHRONIC RENAL FAILURE

Abstract: *Gastric dysfunction in dialysed patients with chronic renal failure.*

Background: Gastric motor functions are disturbed in patients with chronic renal failure (CRF). The aim of this study was to find the relationship between GI symptoms, gastric myoelectrical activity and regulatory peptides (gastrin, motilin, VIP, CCK) in patients with CRF treated with hemodialyses (HD) and peritoneal dialyses (CAPD).

Methods: Gastric myoelectric activity was evaluated with cutaneously recorded electro-gastrographs (EGGs) measurement in: group A: 23 pts with CRF treated with CAPD, group B: 21 pts treated with HD and group C: 48 matched healthy controls. GI symptoms severity was quantified with specially designed questionnaire. The laboratory evaluation of plasma parameters, such as: gastrin, motilin, VIP and CCK was performed.

Results: The patients with CRF treated with CAPD and HD showed a significantly lower percentage of normal 2–4 cpm wave's rhythm in both fasting ($65.3 \pm 29.3\%$ vs $43.5 \pm 35.9\%$ vs $86.4 \pm 10.2\%$) and fed conditions ($72.7 \pm 34.2\%$ vs $69.5 \pm 22.1\%$ vs $89.3 \pm 9.5\%$) in comparison to controls. In the fasting state, none of the healthy controls had an abnormal EGG, whereas the 27 patients with CRF (61.3%) had an abnormal EGG. In the fed state the 18 patients with CRF (40.9%). No significant increase of the dominant power (PDP) after meal in CRF patients was observed. The plasma concentrations of gastrin, CCK were increased in fasted and fed CRF patients, whereas VIP and motilin only in fed state.

Conclusions: The patients with CRF showed impaired gastric myoelectrical activity in response to food and high levels of GI hormones. Gastric dysmotility and high peptides appears to be partially responsible for GI symptoms.

Key words: gastrointestinal symptoms, gastric myoelectrical activity, gastrointestinal hormones, chronic renal disease

INTRODUCTION

Gastrointestinal (GI) symptoms, like nausea, anorexia, bloating and early satiety are common in patients with chronic renal failure (CRF). They could induce malnutrition which is common in dialysed patients. Various nervous and hormonal factors may contribute to the development of these symptoms, but the underlying mechanisms have not been elucidated. A considerable number of circulating hormones and peptides and neural pathways have been implicated in these pathways. The kidney is a major site for the inactivation, degradation, and clearance of a variety of peptide hormones. It has been shown that the uremia increases or decreases GI hormones levels. Fasting plasma concentrations of gastrin-releasing peptide, motilin, neurotensin, pancreatic polypeptide, peptide YY, somatostatin, substance P, and vasoactive intestinal peptide (VIP) were increased in chronic renal failure CRF [1]. Postprandial released gastrin — from gastric antrum — not only has a stimulatory effect on gastric acid secretion, but also on smooth muscle through muscarinic (mainly M3) receptors by acting on the cholinergic component of the gastric nervous plexus. Soffer *et al.* [2] found delayed gastric emptying in dialysed patients; this led to the hypothesis that dyspeptic symptoms, occurring in dialysed patients, are possibly a consequence of impaired gastric motility and subsequently disturbed emptying [3, 4]. Measuring of gastric emptying has been widely accepted as a method of investigating gastric motility, but this measurement only reflects postprandial gastric motor status. Gastric myoelectrical activity recording provides information about both — fasting, as well as fed gastric motor function. There are some reports [5–7] concerning impaired gastric myoelectrical activity induced delayed gastric emptying in renal failure patients, but most of these studies did not distinguish the patients treated with dialysis from those treated conservatively. On the other hand, there are few reports of simultaneous evaluations of gastric myoelectrical activity and gastric emptying that would allow comparison of the respective symptoms with findings observed during the measurements of gastric dysmotility [8–11].

It is well known that cutaneous electrogastrography (EGG) undergoes a change after food ingestion, showing increases in frequency and amplitude compared with preprandial values, but the factors regulating such changes remain to be controversial. Paying special attention to gastrin, motilin and CCK, VIP — the two pair's postprandial and interdigestive motility peptides, we investigated the relationship between gastric myoelectrical activity and GI motility peptides and symptoms that occurred in patients with CRF.

MATERIAL AND METHODS

The study was performed on 48 asymptomatic normal subjects with no history of renal disease or GI disease and 44 symptomatic patients with CRF who were diagnosed by clinical and laboratory measures. Into the study 92 persons were involved, which were divided into three subgroups:

- Group A — 23 pts (14 M, 9 F, age 63 ± 14 years (36–81 yrs)) with chronic renal failure (CRF) treated with continuous ambulatory peritoneal dialysis (CAPD).
- Group B — 21 pts (13 M, 8 F, age 63 ± 12 (37–79 yrs)) with CRF treated with hemodialysis (HD).
- Group C — 48 healthy volunteers (13 M, 35 F, age 63 ± 12 (27–64 yrs)).

In this study the exclusion criteria were: diabetes mellitus, obesity (BMI ≥ 30 kg/m²), cardiovascular diseases (hypertension, coronary artery disease, valvular heart disease, cardiac arrhythmias), not smoking cigarettes at present or

Table 1

Characteristics of the investigated subjects

p < 0.05 statistical significant; * significant differences between group A and B,
 # — between group A and C; & — between group B and C; Group A — with chronic renal failure (CRF) treated with the continuous ambulatory peritoneal dialysis (CAPD);
 Group B — with CRF treated with the hemodialysis (HD); Group C — control group.
 BMI — body mass index, HR — heart rate, BPs — systolic blood pressure,
 BPd — diastolic blood pressure, KT/V — urea, nPCR — normalized protein catabolic rate

PARAMETERS	GROUP A (N = 23)	GROUP B (N = 21)	GROUP C (N = 48)	p
Age [years]	63 ± 14	63 ± 12	50 ± 10	NS
Sex (w/m)	8/7	7/10	6/12	NS
BMI [kg/m ²]	26.9 ± 3.5	23.7 ± 2.1	23.8 ± 0.6	NS
HR (bit/min)	77.3 ± 12.4	75.5 ± 11.6	69.1 ± 11.1	0.03^{#&}
BP _s	120 ± 8.3	127 ± 9	126.5 ± 9	NS
BP _d	80 ± 6	88 ± 8	84 ± 9	NS
CRF Time (months)	83.2 ± 57.3	134.9 ± 108.9	0.04*
Creatinin umol/l	1840 ± 3120	49.5 ± 70	80.1 ± 4.4	0.001^{#&}
KT/V	2.15 ± 2.15	1.49 ± 0.14	NS
ALBUMIN	35.1 ± 5.4	36.0 ± 3.9	58.7 ± 4.2	NS
nPCR	0.94 ± 0.24	NS
TRANSFERRIN g/l	1.96 ± 0.50	1.55 ± 0.33	3.1 ± 0.5	0.04^{#&}

during 3 last months, medications that may interfere with gastric myoelectric measurements, previous surgeries, as well as any pathologies in the GI tract (eg, inflammatory bowel disease), gynecological systems, or chronic diseases.

The following parameters were determined for characteristics of the investigated subjects:

(1) Dialysis adequacy in patients: urea KT/V (a multiple of the volume of plasma cleared of urea divided by the distribution volume of urea) and nPCR (normalized protein catabolic rate) [12, 13].

(2) Long-term nutritional markers: plasma creatinine, albumin, and transferrin. Body mass index (weight in kg/height² in meters) was the nutritional anthropometric method used to evaluate severe obesity (BMI > 30) (Tab. 1).

The study protocol

All subjects were fasted for 6 hr or more prior to the study and had taken no medications with a known effect on GI motility during three days before the study.

In all of investigated subjects were performed the following tests: assessment of GI symptoms, gastric myoelectric activity in the preprandial period and postprandial period after standard meal, and plasma gastrin, CCK, VIP, motilin measurements before and after standard meal.

The study protocol was approved by the Jagiellonian University Bioethical Committee (no. KBET/11/B/2004). All the subjects included in this study were instructed about its purpose and gave/submitted their written consent of participation.

Assessment of GI symptoms

All patients completed a self-administered questionnaire that included eight symptoms (heartburn, abdominal pain, belching, regurgitation, nausea, vomiting, dysphagia, bloating) to assess subjective GI symptoms. The severity of each of these symptoms was scored as: absent (0), mild (1), moderate (2), or severe (3). Factor analyses were also performed.

Electrogastrography (EGG)

Surface electrogastrography was applied to record gastric myoelectrical activity measured in the preprandial period (30 min) and postprandial period (60 min) after standard meal (Nutridrink 300 kcal, Nutricia, Poland). Gastric myoelectrical activity was recorded with three Ag-AgCl standard cutaneous electrodes. One electrode (electrode 1) was placed at the midpoint between the xiphoid and the

navel; one (electrode 2) was placed 5 cm to the left and 3 cm above this point; and a reference electrode (electrode 0) was placed in the lower quadrant close to the left costal margin. The bipolar EGG signal was derived from electrodes 1 and 2 and was amplified using a portable EGG recorder (Digitrapper EGG, Synectics Medical, Inc., Irving, Texas) with low and high cutoff frequencies of 1 and 18 cpm, respectively. Online digitization with a sampling frequency of 1 Hz was performed using an analog-digital converter installed on the recorder, and digitized samples were stored using the adjuvant software (Synectics Medical AB, Stockholm, Sweden). In the analysis of EGG the following parameters were evaluated: percentage of dysrhythmia time (0.5–2 cpm — bradygastria; 4–10 cpm — tachygastria), percentage of normogastria (2–4 cpm), dominant frequency (PDF); dominant power of dominant frequency (PDP). PDF — Period Dominant Frequency was calculated as the average of the dominant frequencies (highest peak) of FFT (Fast Fourier Transform) line. PDP — Period Dominant Power is the power or amplitude of the PDF peak. Changes in the EGG dominant power appear to reflect gastric contractility [14–16].

Biochemical assays

The levels of gastrin, VIP, motilin and CCK were measured before and after standard meal. Blood samples were stored in the 2–8°C and within 2 hours after blood collection were centrifuged to separate the plasma (at 3800 g, at 8°C for 10 minutes). The supernatant was aspirated and stored in the 20°C for a period of 6 hours up to 1 month until the time of analysis. The assessment of the plasma **gastrin** level was performed by using Gastrin I (G 17), (R&D Systems Inc., USA, sensitivity of test 0.7 ng/ml) for automated systems. Analysis of plasma **VIP** concentration was performed by using Human Vasoactive Intestinal Peptide (VIP) kit (Phoenix Pharmaceuticals INC, USA, sensitivity of test 0.13 ng/ml) for automated systems. Analysis of plasma **CCK** levels was performed by using Bender MedSystems test — (Bender MedSystems, Austria, sensitivity of test 1.65 ng/ml) for automated systems. Analysis of plasma **motilin** concentration was performed by using RIA test.

Statistical analysis

Database management and statistical analyses were performed using the Statistica for the Windows, version 7.0 PL (StatSoft the Inc., the Tulsa, Oklahoma, USA). All values are expressed as either percentages or mean \pm SD. The non-normal distribution of the obtained data was demonstrated by Shapiro-Wilk's test. In the case of non-fulfilled criteria of normality, the variables underwent a logarithmic transformation that was then used in the

further statistical analyses. Comparisons between investigated groups for quantitative variables were calculated by using unpaired Student's T-test or Wilcoxon's signed rank test if either distribution was not normal. Statistical analysis of the feeding influences was performed using paired Student's T-test or Mann-Whitney's U test. Associations between the measures of EGG parameters, enterohormons and GI symptoms were studied with the Spearman's correlation coefficients. Statistical significance was assigned for p values of < 0.05 .

RESULTS

Electrogastrography (EGG)

There were observed significant changes of gastric myoelectric activity in patients with CRF (Tab. 2). The patients with CRF being treated with CAPD and HD showed a significantly lower percentage of normal 2–4 cpm wave's rhythm in both — fasting and fed — states in comparison to the healthy controls. The healthy controls had a mean percentage of 2–4 cpm waves of $86.4 \pm 10.2\%$ in the fasting state and $89.63 \pm 9.5\%$ in the fed state. In contrast, the patients treated with CAPD and HD had in the fasting state a mean percentage of 2–4 cpm waves of $65.3 \pm 29.3\%$ vs $43.5 \pm 35.9\%$ and in the fed state $75.7 \pm 34.2\%$ vs $69.5 \pm 22.1\%$ respectively. There was, however, no difference between the two groups of patients in fasting state, although different responses of the power of the EGG at the dominant frequency (PDP) period of dominant power (μV) among the three subject groups were observed. As shown in Table 2, the healthy controls had an average increase from 5.2 ± 1.1 to 6.1 ± 1.4 in the dominant power of the EGG after meal, whereas the patients from groups A and B had no significant increase. Fasted values of PDP remained higher in both patients group — A and B — than those observed in control — group C; 7.2 ± 1.5 and 6.2 ± 2.6 vs 5.2 ± 1.1 . A power ratio of < 1 is believed to correlate with a decreased distal gastric motor response to a meal. In our previous studies, the response of the EGG to a test meal was defined as abnormal if there was no increase in the dominant power of the EGG [14]. Using this definition, it was found that none of the controls (0%) had an abnormal response to the test meal, whereas 6 of the patients with CRF in group A (26%) and 9 of the patients of group B (42.9%) had an abnormal power response to the test meal ($p < 0.01$ in comparison to the controls). The prevalence of an abnormal response of the EGG to the test meal was significantly higher in the patients with CRF than those without ($p < 0.05$). Figure 1 presents percent changes of EGG parameters in response to standard's meal in all investigated groups. It can be seen that the EGG in the healthy subject had more regular 3 cpm

slow waves than that in the both patients' group. The spectra period dominant frequency (PDF) confirmed this observation.

In groups A and B values of PDF (cpm/min) in fasted and fed patients were lower than those observed in the healthy individuals — C group; 2.0 ± 1.2 and 1.8 ± 1.4 vs 2.7 ± 0.6 [cpm/min] respectively, $p = 0.001$ and 1.5 ± 1.3 and 1.3 ± 1.3 vs $2.7 \pm 0.5\%$ [cpm/min] respectively, $p = 0.004$. In previous reports [8], an EGG was defined as abnormal if the percentage of 2–4 cpm slow waves was below 70%. Using this definition, we found that there was a significantly higher prevalence of the abnormal EGG in the patients with CRF than in healthy controls. In the fasting state, none of the healthy controls had an abnormal EGG, whereas 20 patients with CRF (45.5%) had an abnormal EGG: in group A 8 patients (34.8%) and in group B 12 patients (57.1%). In the fed state, all healthy subjects had a normal EGG, whereas 6 patients with CRF (26%), in group A, had an abnormal EGG ($p = 0.005$ in comparison to the controls), and 8 patients with CRF (38.1%), in group B, had an abnormal EGG ($p = 0.002$ in comparison to the controls). However, there was no significant

Table 2

The electrogastrography parameters in all investigated groups before and after standard meal
 $p < 0.05$ statistically significant; * significant differences between group A and B,

— between group A and C; & — between group B and C;

Group A — with CRF treated with the continuous ambulatory peritoneal dialysis (CAPD);

Group B — with CRF treated with the hemodialysis (HD); Group C — control group;

0.5–2 cpm — bradygastria, 2–4 cpm — normogastria, 4–10 cpm — tachygastria,

PDF — period dominant frequency, PDP — period dominant power

	EGG	Group A	Group B	Group C	p
PREPRANDIAL	0.5–2 [cpm]	$9.9 \pm 17.5^{\#}$	$4.1 \pm 5.1^{\&}$	9.2 ± 10.1	0.01^{&}
	2–4 [cpm]	65.3 ± 29.3	43.5 ± 35.9	86.4 ± 10.2	0.01[#]/0.001^{&}
	4–10 [cpm]	8.6 ± 13.8	16.4 ± 28.8	4.3 ± 8.1	NS
	Dysrhythmias	24.5 ± 23.1	$38.5 \pm 33.9^{\&}$	13.5 ± 10.2	0.008^{&}
	PDF [cpm/min]	$2.0 \pm 1.2^{\#}$	$1.8 \pm 1.4^{\&}$	2.7 ± 0.6	0.06[#]/0.03^{&}
	PDP μV^2	$7.2 \pm 1.5^{\#}$	6.2 ± 2.6	5.2 ± 1.1	0.005[#]
POSTPRANDIAL	0.5–2 [cpm]	4.8 ± 8.8	5.9 ± 8.1	6.2 ± 8.4	NS
	2–4 [cpm]	72.7 ± 34.2	$69.5 \pm 22.1^{\&}$	89.3 ± 9.5	0.003^{&}
	4–10 [cpm]	12.2 ± 19.0	9.7 ± 12.3	10.6 ± 9.4	NS
	Dysrhythmias	15.7 ± 26.6	$20.1 \pm 16.9^{\&}$	4.5 ± 5.5	0.04^{&}
	PDF [cpm/min]	$1.5 \pm 1.3^{\#}$	$1.3 \pm 1.3^{\&}$	2.7 ± 0.5	0.004[#]/0.0004^{&}
	PDP μV^2	$7.1 \pm 1.4^{\#}$	6.7 ± 2.4	6.1 ± 1.4	0.07[#]

difference in the prevalence of the abnormal EGG between the two patients' groups, in either fasting or fed state. There was no difference in the percentage of tachygastria between the patients with CRF and healthy group, in both — the fasting and fed state.

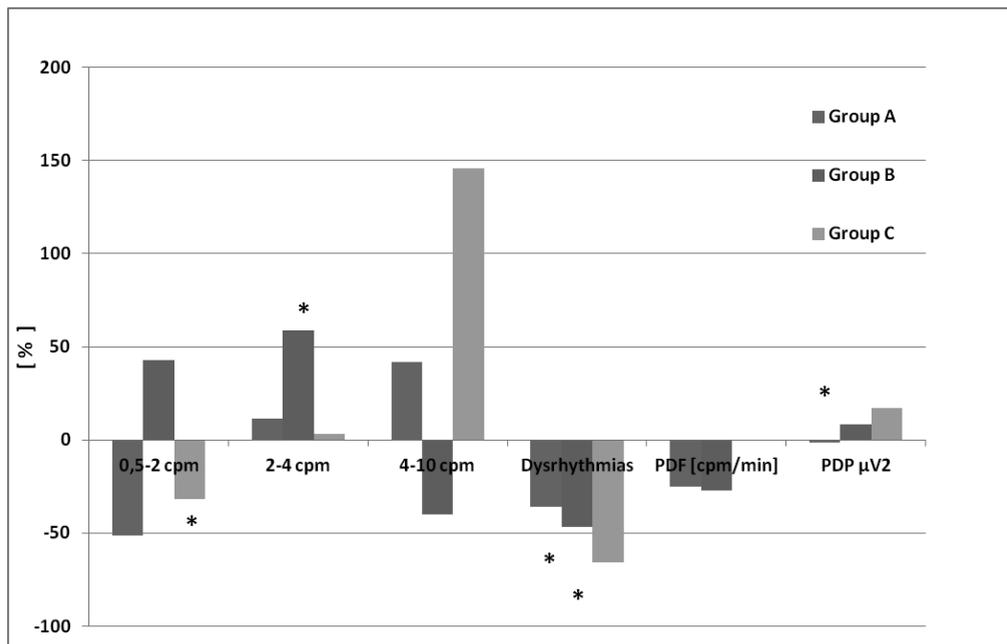


Fig. 1. Percent changes of electrogastrography parameters in response to standard meal in all investigated groups

* — $p < 0.05$; Group A — with CRF treated with the continuous ambulatory peritoneal dialysis (CAPD); Group B — with CRF treated with the hemodialysis (HD); Group C — control group; 0.5–2 cpm — bradygastria, 2–4 cpm — normogastria, 4–10 cpm — tachygastria, PDF — period dominant frequency, PDP — period dominant power

GI peptides

The fasting plasma levels of four chosen GI regulatory peptides (gastrin, CCK, VIP, motilin) were measured by radioimmunoassay in 44 stable patients with CRF receiving peritoneal or hemodialysis treatment regularly and compared to those of 48 healthy matched controls. The plasma concentrations of gastrin, CCK, VIP and motilin were increased in fasted and fed CRF patients and were higher than control, except VIP and motilin in fasting state (Tab. 3).

The level of plasma gastrin

The fasting plasma level of gastrin was higher in group A and B than in the group C (6.57 ± 2.37 vs 4.2 ± 1.6 vs 1.2 ± 0.5 [pg/mL] respectively, $p = 0.001$; Tab. 3). After meal there was noted significant increase in group B and C (Fig. 2).

The level of plasma CCK

The fasting plasma level of CCK was significantly higher in group A and B than in the group C (11.6 ± 9.2 vs 8.1 ± 4.9 vs 3.0 ± 1.5 [pg/mL] respectively, $p = 0.001$; Tab. 3). After meal significant increase in group A and C was observed (Fig. 2).

The plasma level of VIP

The fasting plasma level of VIP was significantly higher in group B than in the group A and C (35.0 ± 18.9 vs 18.2 ± 4.3 vs 26.3 ± 1.9 [pg/mL] respectively, $p = 0.006$; Tab. 3). After meal significant increase in group A and C was found (Fig. 2).

Table 3

Levels of GI hormones in all investigated group
 $p < 0.05$ statistically significant; * significant differences between group A and B,
 # — between group A and C; & — between group B and C;
 Group A — with CRF treated with the continuous ambulatory peritoneal dialysis (CAPD);
 Group B — with CRF treated with the hemodialysis (HD); Group C — control group;
 VIP — Vasoactive Intestinal Peptide, CCK — cholecystokinin

		Group A	Group B	Group C	p
PREPRAN-DIAL	Gastrin	6.57 ± 2.37	4.2 ± 1.6	1.2 ± 0.5	0.001*#&
	CCK	11.6 ± 9.2	8.1 ± 4.9	3.0 ± 1.5	0.01#/0.001&
	VIP	18.2 ± 4.3	35.0 ± 18.9	26.3 ± 1.9	0.006*/0.0001#
	Motilin	197.7 ± 72.3	158.1 ± 87.4	164.0 ± 99.6	NS
POSTPRAN-DIAL	Gastrin	7.0 ± 2.9	4.71 ± 1.9	1.58 ± 0.7	0.001*#&
	CCK	12.7 ± 10.0	8.1 ± 4.9	3.5 ± 1.5	0.01#/0.003&
	VIP	25.1 ± 6.8	35.1 ± 12.1	27.9 ± 6.5	0.01*
	Motilin	316.0 ± 218.9	212.9 ± 107.1	142.0 ± 79.2	0.02#/0.02&

The plasma level of motilin

The fasting plasma level of motilin was significant higher in group A than in the group B and C (197.7 ± 72.3 vs 158.1 ± 87.4 vs 164.0 ± 99.6 [pg/mL] respectively, $p = 0.001$; Tab. 3). After meal significant increase in group A and B was recorded, but in group C plasma level of motilin was decreased (Fig. 2).

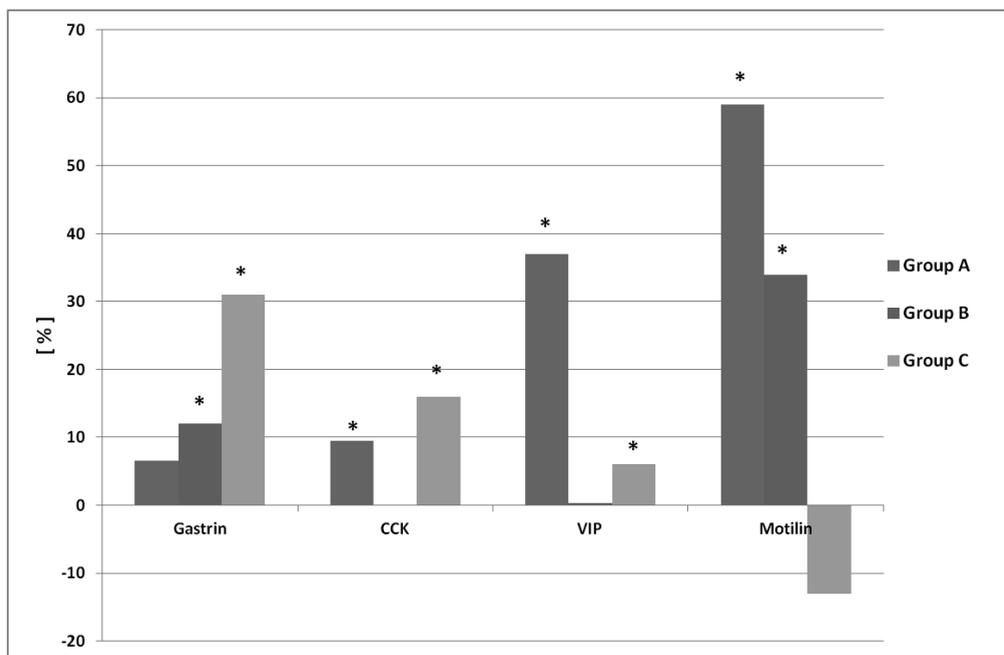


Fig. 2. Percent changes of gastrointestinal hormones in response to standard meal in all investigated groups

* — significant differences between fast and fed state ($p < 0.05$);

Group A — with CRF treated with the continuous ambulatory peritoneal dialysis (CAPD);

Group B — with CRF treated with the hemodialysis (HD); Group C — control group;

VIP — Vasoactive Intestinal Peptide, CCK — cholecystokinin

GI symptoms

Symptoms' Score

Eight symptoms were scored, including; heartburn, abdominal pain, regurgitation, belching, nausea, vomiting, dysphagia and bloating — each graded from 0 to 3, with 0 meaning: no symptoms and 3: the most severe. A total symptoms' score was calculated for each patient, and then an average of total symptoms' score for each group of subjects was computed. The average of total symptoms' score was 0 for the healthy controls, 6 ± 2 for the patients with CRF in group A, and 4 ± 1 for the patients with CRF in group B. There was observed a significant difference in the symptoms' score between the controls and patients, but no significant difference between the two groups of patients with CRF.

Correlation

Symptoms vs EGG. The GI symptoms (belching, nausea, vomiting) were inversely correlated with the dominant power (PDP) ($r = -0.67$; $p = 0.03$) in the CAPD treated patients group and positively correlated with tachygastria ($r = 0.78$; $p = 0.03$), bradygastria ($r = 0.78$; $p = 0.03$) and dysrhythmia in pre- ($r = 0.89$; $p = 0.006$) and postprandial ($r = 0.77$; $p = 0.03$) period in the HD treated patient group.

Symptoms vs enterohormones. In the group of patients treated with CAPD, the nausea negatively correlated with preprandial gastrin ($r = -0.89$; $p = 0.04$) and positively with VIP ($r = 0.89$; $p = 0.04$). We noted a positive correlation between belching, nausea and postprandial VIP level ($r = 0.74$; $p = 0.02$) and between belching and preprandial gastrin ($r = 0.9$; $p = 0.004$) in the HD treated group.

EGG vs hormones. In the group of patients treated with HD, the plasma VIP level was inversely correlated with preprandial PDP ($r = -0.5$; $p = 0.04$) and positively VIP with normogastria ($r = 0.54$; $p = 0.02$) and motilin with preprandial PDP ($r = 0.5$; $p = 0.04$). Postprandial CCK was positively correlated with bradygastria ($r = 0.66$; $p = 0.004$). In CRF group with CAPD we observed positive correlation between postprandial plasma CCK level ($r = 0.55$; $p = 0.04$), motilin level and dysrhythmia ($r = 0.62$; $p = 0.01$) and negative correlation between preprandial CCK and tachygastria ($r = -0.55$; $p = 0.03$) and between preprandial VIP plasma level and PDF ($r = -0.6$; $p = 0.02$).

DISCUSSION

This study was undertaken to evaluate the pathophysiological importance of changes in gastric myoelectric activity and peptides levels in hemodialysed and peritoneodialysed CRF patients. We have found that:

(1) Patients with CRF showed a significantly lower percentage of normal 2–4 cpm waves in both fasting and fed states. There was a significantly higher prevalence of the abnormal EGG (the percentage of normogastria below 70%) in the patients with CRF in both fasting and fed states.

(2) In comparison to healthy controls, the EGG parameters obtained from patients with CRF showed higher values than in control and there wasn't also observed any increase in the amplitude of the EGG after the test meal. The prevalence of an abnormal response of the EGG to the test meal (no increase or a decrease in EGG dominant power after the test meal) was significantly higher in patients with CRF.

(3) There was a significant increase in the dominant frequency in the controls after the test meal; but such a phenomenon was not observed in patients with CRF.

(4) There was no significant difference in the regularity of the gastric slow wave between the patients treated with CAPD and those treated with HD. The prevalence of an abnormal response to the test meal in EGG dominant power was significantly higher in the group of patients treated with CAPD than in the one treated with HD.

(5) No significant difference was found in the symptoms' scores between the two groups of patients, although the patients treated with CAPD had a slightly higher score.

(6) The plasma concentrations of gastrin, CCK were increased in fasted and fed CRF patients, VIP and motilin only in fed stage. They were higher than control.

(7) Correlation between elevated serum enetrohormons levels (gastrin, VIP, CCK, motilin), GI symptoms and gastric myoelectrical activity disturbances was found.

In this study, we used EGG and evaluation of serum GI peptides levels to assess gastric function. Still, there is a lack of data about gastric myoelectrical activity and GI peptides in patients with CRF [17–19]. The studies conducted by Ravelli *et al.* [4, 5] were the first experiments investigating gastric myoelectrical activity in CRF patients. Their studies were performed in pediatric patients with CRF, and gastric myoelectric activity was also recorded using EGG. The studied patients were children with severe CRF and symptoms of anorexia and vomiting. The majority of patients were having gastric dysrhythmias, including both bradyarrhythmia and tachyarrhythmia. However, no quantitative figure, such as the percentage of 2–4 cpm slow waves was given in that study. Jebink

et al. [6], performed a study, where there was recorded gastric myoelectrical activity in adult patients with CRF and then analyzed using a more quantitative method. The consistency between this current study and the previous studies by Ravelli *et al.* suggests that noninvasive EGG is a reliable technique for the measurement of gastric myoelectric activity.

In our study, all patients suffered from end-stage renal disease with severe uremia and were treated with using CAPD or HD. Furthermore, our study is the first to simultaneously measure gastric myoelectric activity and serum GI hormones' levels in patients with CRF. We found that in CRF patients there occurred a specific pattern of gastric hypomotility, including disturbed gastric myoelectrical activity and increased GI hormones, compared to healthy controls. In addition, a significant correlation was observed between certain EGG parameters and GI hormones, as well as GI symptoms. Gastric myoelectrical activity is an essential trigger for predicting gastric emptying and contractility. Chen *et al.* [8, 9] showed that postprandial gastric dysrhythmia predicted delayed gastric emptying, while abnormality in the postprandial EGG power predicted delayed gastric emptying with an accuracy of more than 70%. Other studies [20, 21] showed that disturbance of the postprandial increase in the EGG power reflected gastric hypocontraction. These studies support our results.

The EGG patterns in healthy subjects usually show specific responses to a test meal [11]. These include both, a substantial increase in the amplitude or dominant power and a significant increase in the dominant frequency of the EGG test after a meal. These phenomena were also observed in the normal subjects in our study. However, the fasted dominant power of the EGG was higher in both patients' groups with CRF than in control group. After a meal, PDP increased, although — it was not as substantial as reported in the control [6].

Several studies have suggested the importance of tachygastric in the genesis of dyspeptic symptoms, including nausea and bloating [22, 23]. In Chen *at al.* studies, the lower percentage of normogastria and a smaller increase/decrease in the PDP of fed pattern indicated the myoelectrical gastroparetic response [24, 25]. Using such definition based on those results, he showed that described disturbances in fed pattern may predict delayed gastric emptying with an accuracy of 78%. That is, according to those data, that a majority of patients with an abnormal postprandial EGG or an abnormal response to the test meal have delayed gastric emptying [11]. Based on such conclusion, we may interpret our data in a way that we suggest that most of the patients with CRF how the pattern of delayed gastric emptying after the meal. And such a point of view could be supported with the results of other studies [2, 26–28].

In the present study, there was observed a high prevalence of GI symptoms in patients with CRF. We found that patients with both, abnormal EGG and high GI hormones levels showed a simple relationship between GI symptoms'

scores and dysrhythmias and inverse correlation between GI symptoms and PDP. However, the percentage of tachygastrica and bradygastrica did not differ significantly between CRF patients and controls in postprandial period, while the preprandial percentage of bradygastrica was higher in CRF patients. Our data support previous reports and confirm that gastric dysmotility might be considered as an important etiologic factor of dyspeptic symptoms.

The kidney is a major site of inactivation of GI polypeptides (e.g. gastrin, CCK, neurotensin and pancreatic polypeptide) involved in the modulation of GI motility and the regulation of hunger and satiety. Thus, serum levels of several hormones are significantly raised as a consequence of renal failure and can be reversed to normal by renal transplantation.

In healthy subjects, the intramuscular injection of tetragastrin significantly increased EGG frequency dose-dependently, but caused no significant change in amplitude [29]. These results suggest that the increase in endogenous gastrin release is one of the mechanisms which underlie the increase in EGG frequency after food ingestion. In our studies, despite of high plasma gastrin fasting level in CRF patients, food did not significantly alter gastrin release in HD patients. Sirinek *at al.* [1], partially confirmed our results showing that mean serum amylase, lipase, secretin, and gastrin levels were found meaningfully decreased according to the beginning values at third months of the CAPD and HD treatment. However, they were higher than control group.

VIP paracrine release is a neuromodulator of the sphincters actions. Its influences include relaxation of gastric and intestinal smooth muscles and inhibition of gastric secretions. In uremic patients, wide variations of plasma concentrations of VIP have been reported. Kabemura *at al.* [30] found that in patients treated with HD, the plasma concentrations of the main GI peptides increased. In our study, in the group treated with CAPD, VIP level was lower than control and had significantly increased after feeding — in contrary to the group treated with HD, where it was higher than control. Sharkaway *at al.*, found similar to our relationship high difference plasma VIP levels in uremic patients where 5 times higher than control [31]. There exists also, inverse correlation between VIP levels and manometry. VIP was low in subgroup with normal manometry, but its levels were elevated in patients with dysmotility. Similarly to our study, VIP levels were elevated in patients with bradygastrica and tachygastrica.

CCK is early satiation's factor [32]. CCK binds to receptors on vagal afferents and mucosa and induces gastric relaxation and slow gastric emptying. CCK is metabolized by the kidney [33], consequently its serum levels can be raised in renal failure [1]. Given that CCK accumulates in CRF and retards gastric emptying [34], it may be partly responsible for the premature satiation effect. Degree of elevation was correlated with the severity of renal damage. In our study, CCK levels were significantly higher in CRF patients and positively

correlated with bradycardia and dysrhythmia, as well as with satiety [35]. CCK has recognized anorectic effect, although this direct association might be lacking because of an abnormal stimulation of these CCK–glucose feedback (trypsin) due to continuous peritoneal not bowel mucosa lavage. This suggests that CCK level could be an immediate food intake marker in CAPD patients.

CRF is the clinical state to be associated with elevated plasma motilin concentrations [36–37]. Our study confirmed previous findings that the fasting plasma levels of motilin was significantly higher in patients treated with CAPD than those treated with HD and the control, as well as that after meal it had further increased. Shima *et al.* [38] had found that hypermotilinemia and the accumulation of this high molecular weight motilin in patients with CRF suggest that the kidney plays some role in the elimination of motilin, and further, that the clearance of the high molecular motilin is more dependent on renal function than that of authentic motilin.

The above observations indicate that gut hormones' release, in particular response to CCK, is likely to have pathogenetic significance in the GI dysmotility observed in CRF patients [39]. Increased levels of motilin and PYY may exacerbate impaired energy intake by slowing gastric emptying in patients in whom nutrition is already compromised.

In summary, this is the first study to evaluate gastric myoelectric activity and GI hormones simultaneously in patients with end-stage renal disease treated with hemodialyses and peritoneal dialyses. CRF patients showed impaired gastric myoelectrical activity suggesting dysmotility and mostly higher levels gastrointestinal peptides which may be responsible for dysmotility and symptoms.

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CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Sirinek K.R., O'Dorisio T.M., Gaskill H.V., Levine B.A.: Chronic renal failure: effect of haemodialysis on gastrointestinal hormones. *Am J Surg.* 1984, 148: 732–773. — 2. Soffer E.E., Geva B., Helman C., Avni Y., Bar-Meir S.: Gastric emptying in chronic renal failure patients on hemodialysis.

J Clin Gastroenterol. 1987, 9: 651–653. — **3.** *Brown-Cartwright D., Smith H.J., Feldman M.*: Gastric emptying of an indigestible solid in patients with end-stage renal disease on continuous ambulatory peritoneal dialysis. *Gastroenterology*. 1988, 95: 49–51. — **4.** *Ravelli A.M., Ledermann S.E., Trompeter R.S., Bisset W.M., Milla P.J.*: Mechanisms of anorexia and vomiting in children with chronic renal failure. *Gut*. 1992, 33: 70–78. — **5.** *Ravelli A.M., Ledermann S.E., Trompeter R.S., Milla P.J.*: Gastric antral myoelectrical activity in children with chronic renal failure. [In:] *Electrogastrography: Principles and Applications*. Chen J., McCallum R.W. (eds). New York, Raven, 1994: 411–418. — **6.** *Jebbink H.J., Bruijs P.P., Bravenboer B., Akkermans L.M., van Berghe-Henegouwen G.P., Smout A.J.*: Gastric myoelectrical activity in patients with type I diabetes mellitus and autonomic neuropathy. *Dig Dis Sci*. 1994, 39(11): 2376–2383. — **7.** *Dumitrascu D.L., Barnert J., Kirschner T., Weinbeck M.*: Antral emptying of semisolid meal measured by real-time ultrasonography in chronic renal failure. *Dig Dis Sci*. 1995, 40(3): 636–644. — **8.** *Chen J., McCallum R.W., Richards R.*: Frequency components of the electrogastrogram and their correlations with gastrointestinal contractions in humans. *Med & Biol Eng & Comput*. 1993, 31: 60–67. — **9.** *Chen J.D.Z., Richards R.D., McCallum R.W.*: Identification of gastric contractions from the cutaneous electrogastrogram. *Am J Gastroenterol*. 1994, 89: 79–85. — **10.** *Sun W.M., Smout A., Malbert C., Edelbroek M.A.L., Jones K., Dent J.*: Relationship between surface electrogastrography and antropyloric pressures. *Am J Physiol*. 1995, 268: 424–430.

11. *Parkman H.P., Miller M.A., Trate D., Knight L.C., Urbain J.L., Maurer A.H.*: Electrogastrography and gastric emptying scintigraphy are complementary for assessment of dyspepsia. *J Clin Gastroenterol*. 1997, 24: 214–219. — **12.** *Black D.A.K.*: Diagnosis and renal disease. [In:] *Renal Disease*, 4th ed. DAK Black (ed). St. Louis, Missouri, Blackwell, 1980. — **13.** *Coe F.L., Brenner B.M.*: Approach to patients with diseases of the kidneys and urinary tract. [In:] *Harrison's Principles of Internal Medicine*, 11th ed. New York, McGraw-Hill, 1987. — **14.** *Parkman H.P., Hasler W.L., Barnett J.L., Eaker E.Y.*: Electrogastrography: a document prepared by the gastric section of the American Motility Society Clinical GI Motility Testing Task Force. *Neurogastroenterol Motil*. 2003, 15: 89–102. — **15.** *Tabor S., Thor P.J., Pitala A., Laskiewicz J.*: Wartość parametrów elektrogastrograficznych w ocenie czynności mioelektrycznej żołądka. *Folia Med Crac*. 1999, 40(3–4): 27–42. — **16.** *Furgala A., Mazur M., Jabłoński K., Mądrozskiewicz D., Ciećko-Michalska I., Thor P.J.*: Myoelectric and autonomic nervous system activities in patients with irritable bowel syndrome. *Folia Med Crac*. 2008, 49 (3–4): 49–58. — **17.** *Lin X., Mellow M.H., Southmayd L., Pan J., Chen J.D.Z.*: Impaired gastric myoelectrical activity in patients with chronic renal failure. *Dig Dis Sci*. 1997, 42: 898–906. — **18.** *Ko C.W., Chang C.S., Wu M.J., Chen G.H.*: Transient impact of hemodialysis on gastric myoelectrical activity of uremic patients. *Dig Dis Sci*. 1998, 43: 1159–1164. — **19.** *Lee S.W., Song J.H., Kim G.A., Yang H.J., Lee K.J., Kim J.M.*: Effect of dialysis modalities on gastric myoelectrical activity in end-stage renal disease patients. *Am J Kidney Dis*. 2000, 36: 566–573. — **20.** *Hamilton J.W., Bellahsene B.E., Reichelderfer M.*: Human Electrogastrograms. Comparison of surface and mucosal recording. *Dig Dis Sci*. 1986, 31: 33–39.

21. *Chen J.D.Z., Pan J., McCallum R.W.*: Clinical significance of gastric myoelectrical dysrhythmia. *Dig Dis Sci*. 1995, 13: 275–290. — **22.** *You C.H., Chey W.Y., Lee K.Y.*: Gastric and small intestinal myoelectrical dysrhythmia associated with chronic intractable nausea and vomiting. *Ann Intern Med*. 1981, 95: 449–451. — **23.** *Gerdof H., Vanderschee E.J., Vanblank E.M.*: Electrogastrographic study of gastric myoelectrical activity in patients with unexplained nausea and vomiting. *Gut*. 1986, 27: 799–808. — **24.** *Chen J., Schirmer B.D., McCallum R.W.*: Serosal and cutaneous recordings of gastric myoelectrical activity in patients with gastroparesis. *Am J Physiol*. 1994, 266: 90–98. — **25.** *Chen J., McCallum R.W.*: Gastric slow wave abnormalities in patients with gastroparesis. *Am J Gastroenterol*. 1992, 87: 477–482. — **26.** *Dumitrascu D.L., Barnert J., Kirschner T., Weinbeck M.*: Antral emptying of semisolid meal measured by real-time ultrasonography in chronic renal failure. *Dig Dis Sci*. 1995, 40(3): 636–644. — **27.** *Brown-Cartwright D., Smith H.J., Feldman M.*: Gastric emptying of an indigestible solid in patients with end-stage

renal disease on continuous ambulatory peritoneal dialysis. *Gastroenterology*. 1988, 95: 49–51. — **28.** *McNamee P.T., Moore G.W., McGeown M.G., Doherty C.C., Collins B.J.*: Gastric emptying in chronic renal failure. *Br Med J*. 1985, 291: 310–311. — **29.** *Yada S., Komi N.*: Effects of cholecystokinin-octapeptide and tetragastrin of the contractile activities of the stomach, duodenum and papilla of Vater. *Jpn J Smooth Muscle Res*. 1988, 14: 101–111. — **30.** *Kabemura T., Mishawa T., Chikiiwa Y., Nasu T., Nawata H.*: Substance P, Vasoactive Intestinal Polypeptide, and gastrin catabolism in canine liver and kidney. *Dig Dis Sci*. 1992, 37(11): 1661–1665.

31. *El Sharkawy M., Aziz A., El Saed K., Aref H.*: Plasma vasoactive intestinal peptide in dyspeptic uremic patients. 48th Congress of the European Renal Association and European Dialysis and Transplant Association 2011, 23–26 Jun 2011, Sa-180. F1000 Posters 2011, 2: 1040; <http://f1000.com/posters/browse/summary/1798>. — **32.** *Fujii K.*: Physiological control mechanism of gastrointestinal motility. *Jpn J Smooth Muscle Res*. 1990, 26: 93–106. — **33.** *Matson C.A., Watter M.F., Kuijper J.L., Egle D.S.*: Synergy between leptin and cholecystokinin (CCK) to control daily caloric intake. *Peptides*. 1997, 18: 1275–1278. — **34.** *Khoo J., Rayner K., Feinle-Bisset C., Jones K.L., Horowitz M.*: Gastrointestinal hormonal dysfunction in gastroparesis and functional dyspepsia. *Neurogastroenterology Motil*. 2010, 22: 1270–1278. — **35.** *Budzyński A., Bobrzyński A., Lorens K., Konturek P.C., Thor P., Konturek S.J.*: The influence of CCK on gastric myoelectrical activity in duodenal ulcer patients following Hp eradication — an electrogastrographic study. *J Physiol Pharmacol*. 2002, 53(2): 171–182. — **36.** *Sirinek K.R., O'Dorisio T.M., Gaskill H.V., Levine B.A., Borazan A., Cavdar Z., Saglam F.*: The effect of renal replacement therapies on serum gastrointestinal. *System Hormones*. 2007, 29(8): 1019–1023. — **37.** *McCallum R.W., Cynshi O.*: Investigative Team. Clinical trial: effect of mitemincal (a motilin agonist) on gastric emptying in patients with gastroparesis — a randomized, multicentre, placebo-controlled study. *Aliment Pharmacol Ther*. 2007, 26: 1121–1130. — **38.** *Shima K., Shin S., Tanaka A., Hashimura E., Nishino T., Imagawa K., Kumahara Y., Yanaihara N.*: Heterogeneity of plasma motilin in patients with chronic renal failure. *Horm Metab Res*. 1980, 12(7): 328–331. — **39.** *Nguyen N.Q., Fraser R.J., Bryant L.K., Chapman M.J., Wishart J., Holloway R.H., Butler R., Horowitz M.*: The relationship between gastric emptying, plasma cholecystokinin and peptide YY in critically ill patients. *Crit Care*. 2007, 11: R132 (doi:10.1186/cc6205).

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