

CLINICAL STUDY

The Effect of Renal Replacement Therapies on Serum Gastrointestinal System Hormones

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Background. 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 gastrointestinal system (GIS) hormones. Moreover, studies investigating the serum GIS hormones levels in chronic renal failure (CRF) were conducted mainly in a particular period of the renal replacement therapy, and the changes caused by continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD) could not be fully demonstrated. In this study, we investigated the effect of CAPD and HD on serum GIS hormones (amylase, lipase, trypsinogen, and gastrin) levels in CRF patients who were diagnosed for the first time. **Methods.** Serum amylase, lipase, trypsinogen, and gastrin levels were measured in 36 patients who were just diagnosed with CRF, 22 patients with CAPD and 14 patients with HD. GIS hormones of these patients were measured before treatment and three months from the beginning of CAPD and HD treatment. As the control group, 20 normal healthy cases with well-matched age and gender were used. **Results.** The 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. **Conclusion.** In patients receiving CAPD or HD as renal replacement therapy, GIS hormone levels were found to be lower, albeit higher than the healthy control group.

Keywords chronic renal failure, amylase, lipase, trypsinogen, gastrin

INTRODUCTION

Various functional and structural abnormalities are commonly encountered in gastrointestinal system (GIS) of chronic renal failure (CRF) patients. Main disturbances are stomatitis, gastritis, duodenitis, delayed motility, increased bowel mucosal permeability, and microbiological flora alteration.^[1–4] The pathophysiologic characteristics of these disturbances remain unclear, but increased levels of circulating gastrointestinal hormones may contribute to these dysfunctions.^[5]

The GIS is a main source of biologically active regulatory peptides. These peptides are formed in endocrine cells and/or in nerve fibers throughout the human intestinal system and in the pancreas.^[6–8]

The kidney is a major site for the degradation, inactivation, and clearance of a variety of peptide hormones.^[1,2] Many of these peptides are catabolized by the kidney, and their baseline plasma levels are increased in uremia.^[2,5,7] In addition to GIS changes described in uremia, continuous ambulatory peritoneal dialysis (CAPD) may alter the GI function through different mechanisms. These include the mechanical effect of CAPD fluid that increases intraabdominal pressure, as well as structural changes of parietal and visceral peritoneum.^[1,9]

Various investigators reported changes in serum GIS hormone levels in patients with CRF receiving hemodialysis (HD) or CAPD treatments.^[1,10–14] Contradictory results are available from studies examining the effect of dialysis on GIS hormone levels,^[10,15,16] often due to a small number of patients, different renal replacement therapies used, and different stages of renal failures studied.^[5] Moreover, the

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studies investigating the serum GIS hormones levels in CRF were conducted mainly in a particular period of the renal replacement therapy, and the changes caused by CAPD and HD could not be fully demonstrated. In this study, we investigated the effect of CAPD and HD on serum GIS hormones (amylase, lipase, trypsinogen, gastrin) levels in CRF patients who were diagnosed for the first time.

SUBJECTS AND METHODS

This study was conducted by first getting permission from the local ethic committee. In all, 36 (15 male, 21 female) consecutive patients who were diagnosed in our center as having CRF for the first time were included, 22 patients CAPD (9 male, 13 female) and 14 patients HD (6 male, 8 female). Twenty (11 male, 9 female) healthy subjects with appropriate age were enrolled as the control group.

The patients who had prior stomach surgery; who had taken eradication treatment for *H. pylori*; or who had taken antibiotics, proton pump inhibitors (PPI), H_2 receptor blockers, or bismuth compounds in the last month were excluded from the study. In all patients, *H. pylori* was investigated serologically.

The demographic characteristics and the CRF causes of the patients are shown in Table 1. Blood samples were taken from a superficial vein on the forearm for the measurement of serum amylase, lipase, trypsinogen, gastrin levels, and biochemical parameters from the cases before and after three months of CAPD and HD treatment, as well as from 20 healthy subjects who were well matched for age and gender. In the HD patients, the blood samples were taken before the half-hour HD session. The venous blood samples taken from the subjects of the whole group

were stored in deep freeze at -20°C until the time of measurement.

HD with bicarbonate was administered for four hours three times a week by using Hollow-Fiber dialyzers with polysulphone membrane and 1.2m^2 of surface area for the subjects in the HD group. In the CAPD cases, 2.0 liters of peritoneal dialysis solution with 1.36% and when necessary with 3.86% of glucose content was used 3–4 times a day. To all subjects, a CRF diet containing 30–35 kcal/kg/day energy, 1.2–1.4 g/kg/day protein, 1000–1500 mg/day calcium, 600–700 mg/day phosphorus, and 200–250 mg/day magnesium was administered. In addition, the subjects were using erythropoietin, iron preparations, and calcium acetate as phosphorus binder. The biochemical parameters were measured in our central laboratory.

The fasting serum total alpha amylase (normal range 25–125 IU/L) and lipase (normal range 13–160 IU/L) was determined with the enzymatic assay (Roche, Mannheim, Germany).

The fasting serum trypsinogen (normal: 20–90 $\mu\text{g/L}$; ELISA, Biotrin International Ltd., Dublin, Ireland) and gastrin (normal: 25–125 pg/mL; RIA, Dainabot, Tokyo, Japan) were also analyzed.

Statistical Method

In the CAPD and HD patients, paired t-test was used for the comparisons of the baseline and three-month values. In the comparison made between the CAPD and HD groups and control group (according to their appropriateness), an ANOVA or Kruskal Wallis analysis was used. When differences were detected in these analyses, to demonstrate between which subgroups the differences existed, the Tukey test was done for the ANOVA group and the Bonferonni-corrected Mann Whitney U test was done for Kruskal Wallis test group.

RESULTS

The mean serum amylase, lipase, secretin, gastrin, trypsin, VIP, and CCK levels of the CAPD and HD patients—both before CAPD and HD and after three months of CAPD and HD treatment—and normal healthy subjects, as well as a statistical analysis, are shown in Table 2.

Serum amylase, lipase, trypsinogen, and gastrin levels in both CAPD and HD patients were higher than non-uremic healthy control group prior to the therapy ($p < 0.001$). Serum amylase ($p < 0.05$), lipase ($p < 0.05$), gastrin ($p < 0.001$), and trypsinogen ($p < 0.001$) levels in both CAPD and HD groups were obviously lower at three months than the pretreatment levels.

Table 1

Demographic characteristics of the groups and primary diseases of the patients

	CAPD	HD	Control
Age (years)	41 $\pm$ 8	43 $\pm$ 9	43 $\pm$ 7
Gender (F/M)	13/9	8/6	9/11
Primary disease			
Diabetic nephropathy	8	5	
Chronic glomerulonephritis	5	3	
Hypertensive nephropathy	5	1	
Chronic pyelonephritis	—	1	
Obstructive nephropathy	3	2	
Polycystic renal disease	—	1	
Amyloidosis	—	1	
Etiology is not known	1	—	
Total	22	14	20

Table 2
The mean serum levels of GIS hormones in the groups

	CAPD	HD	Control	<i>p</i> value
Amylase (IU/L)	180.1 ± 63.4	176.0 ± 62.5	87.62 ± 14.3	NS, * <0.001 [†]
Amylase, third month (IU/L)	108.4 ± 41.6	112.8 ± 44.6		NS*
Lipase (IU/L)	140.5 ± 49.8	141.0 ± 52.1	60.7 ± 23.2	NS, * <0.001 [†]
Lipase, third month (IU/L)	100.3 ± 41.6	103.5 ± 39.8		NS*
Trypsinogen (μg/L)	288.2 ± 45.6	291.3 ± 48.5	52.4 ± 21.1	NS, * <0.001 [†]
Trypsinogen, third month (μg/L)	170.4 ± 57.1	201.6 ± 63.5		<0.05*
Gastrin (pg/mL)	258.4 ± 50.2	260.6 ± 52.0	148.8 ± 37.4	NS, * <0.001 [†]
Gastrin, third month (pg/mL)	183.7 ± 44.6	209.8 ± 44.0		<0.05*

*Continuous ambulatory peritoneal dialysis versus hemodialysis.

[†]Continuous ambulatory peritoneal dialysis versus control group, hemodialysis versus control group.

NS = not significant.

Table 3
The number and percentage of patients with elevated GIS hormone levels in the groups

	Before CAPD, n (%)	CAPD third month, n (%)	Before HD, n (%)	HD third month, n (%)
Amylase	12 (55%)	7 (32%)	8 (57%)	3 (21%)
Lipase	10 (46%)	9 (41%)	5 (36%)	3 (21%)
Trypsinogen	13 (59%)	11 (50%)	7 (50%)	5 (36%)
Gastrin	17 (77%)	13 (59%)	10 (71%)	9 (64%)

The decrease in serum gastrin and trypsinogen levels in CAPD group was greater than in the HD group at the third month of therapy. These hormones were lower in CAPD group than in HD group at the third month of therapy ($p < 0.05$).

GIS hormone levels at the third month of the therapy were still higher in both CAPD and HD groups than the healthy control group ($p < 0.001$).

The number and percentage of patients with an elevated hormone levels in both CAPD and HD groups at the baseline and at the third month of therapy are shown in Table 3. The number of patients with an elevated hormone levels in both CAPD and HD groups were observed to decline with the initiation of therapy.

No episode of acute pancreatitis in any subject developed in the first three months. Two peritonitis episodes developed within one month in two patients in CAPD group. There was no intraabdominal event in any subject within the last two months.

H. pylori infection was found positive in 17 of the 22 CAPD patients (77%), 11 of the 14 HD patients (78%), and 15 of the 20 normal healthy subjects (75%). There were no differences between the groups in *H. pylori* positivity. No eradication was attempted in *H. pylori* positive cases.

DISCUSSION

Several polypeptide hormones involved in the modulation of gastrointestinal motility (e.g., gastrin, CCK, motilin, VIP) and the regulation of hunger and satiety (e.g. glucagon, CCK) are significantly raised as a consequence of renal insufficiency, and can be reverted to normal by renal transplantation. Furthermore, several other humoral abnormalities (e.g., hypercalcemia, hypokalemia, acidosis, etc.) are not uncommon in CRF. By directly affecting the smooth muscle of the gut or stimulating particular areas within the central nervous system, all of these humoral alterations may well play a major role in the gastrointestinal dysmotility, anorexia, nausea, and vomiting in the patients with CRF.^[1,2,10,17]

In studies on the effect of both CAPD and HD on GIS hormone levels in CRF patients, different results have been obtained.^[1,5,11,18] We think that these differences might particularly arise from the lack of comparison of levels of GIS hormones prior to the dialysis treatment with the baseline values in the same subjects, which was the impetus behind the present study.

The results we obtained in uremic patients prior to the renal replacement therapy are consistent with the data in the literature pointing out that GIS hormone levels increase

in uremic patients. For the first time in the literature, we investigated the changes in hormone levels in these patients three months after the initiation of CAPD or HD as a renal replacement therapy. In our subject group, both in CAPD and HD subgroups, an obvious decrease in serum amylase, lipase, trypsinogen, and gastrin, levels were observed. However, no GIS hormone in the CRF group decreased to levels of control group with a normal renal function. A decrease in serum gastrin and trypsinogen levels in the CAPD group was more evident than in the HD group.

Pancreatic abnormalities have been demonstrated in CRF patients and found at autopsy in 56% of long-term CAPD patients.^[4,19,20] Increased levels of pancreatic enzymes have been reported in patients with CRF and described in impaired urinary excretion.^[21–24] Plasma amylase and lipase concentrations have been reported to be usually moderate elevated in CRF patients.^[21–24] A plasma amylase concentration exceeding three times the upper limit of normal is often considered to be caused by either pancreatitis or other abdominal event.^[21,23,25–28] Gupta et al.^[26] found normal plasma amylase concentrations in 60% of patients who were started on CAPD treatment. In our study, amylase levels were high initially in 55% of CAPD patients and still high in 32% of the cases at the end of three months, whereas it was high initially in 57% of the HD patients and remained high in 21% at the end of three months. Lipase levels were high in 46% of the CAPD patients at the beginning and remained high in 41% of the cases at the end of three months. Meanwhile, in the HD group, they were high in 36% of the patients at the beginning yet still higher in 21% of the cases at the end of three months. In our study, the values at the end of three months were much lower than baseline in both CAPD and HD groups. Though amylase and lipase levels in both groups dropped to normal levels at the third month of the therapy, they were still higher than those of healthy control group.

There are a few studies in the literature regarding trypsinogen in CRF patients. It has been reported that trypsinogen levels are higher in CRF patients undergoing CAPD or HD treatments. It has been suggested that the higher levels of trypsinogen may result from oversecretion of this hormone from pancreas, a decrease in renal clearance, or the combination of both in uremic patients.^[29–32] Kimmel et al.^[29] reported that serum trypsinogen levels remains similar in CAPD and HD groups but still higher than in control group. On the other hand, in our study, mean serum trypsinogen levels both in CAPD and HD groups were evidently higher than the control group both at the baseline and at the third month. However, it was lower in CAPD group than the HD group at the third month of therapy. The possible reason for this may be the incomplete loss of renal residual functions within the first

three months in CAPD patients. We think that renal clearance is more important in serum trypsinogen level elevation in uremic patients.

Gastrin is the peptide most studied, and a high incidence of peptic ulcer disease has been documented in patients with CRF^[7] and also gastric acid hypersecretion.^[7,33–35] Serum gastrin levels are generally elevated in uremia, though there is much variation. Many patients had normal levels, but 10% had values within the gastrinoma range.^[2,36] It has been shown in previous studies that the elevation in serum gastrin levels remains constant in patients undergoing dialysis.^[37] Gastric acid suppression, a decrease in renal clearance of gastrin, an increase in concentration of gastrin-releasing peptid, and *H. pylori* infection are all responsible for elevated gastrin levels in HD patients.^[37–39] We held the higher prevalence of *H. pylori* infection responsible in our study for the elevation of gastrin levels in control group with normal renal functions. Serum gastrin level, though obviously decreasing at the third month of the therapy with both dialysis methods, was higher than the healthy control group.

As a result, it was found that serum amylase, lipase, trypsinogen, and gastrin levels are quite high in uremic patients. Although an evident decrease in GIS hormones was observed at three months of treatment of both CAPD and HD patients, the levels were still higher than the non-uremic patients. We suggest that the reason of lower levels of some hormones in CAPD patients than the HD patients may depend on the fact that residual renal functions in CAPD patients are more preserved, as well as the more stable course of uremic toxins than HD.

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