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The Effects of Continuous Ambulatory Peritoneal Dialysis and Hemodialysis on Serum Pepsinogen Concentrations in Patients with Chronic Renal Failure

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Department of Gastroenterology, [1]Internal Medicine, [2]Department of Biochemistry, Zonguldak Karaelmas University Faculty of Medicine, Zonguldak, and [3]Department of Nephrology, Kocaeli University Faculty of Medicine, Kocaeli, Turkey

AYDEMIR, S., BORAZAN, A., ACIKGOZ, S., USTUNDAG, Y. and YILMAZ, A. *The Effects of Continuous Ambulatory Peritoneal Dialysis and Hemodialysis on Serum Pepsinogen Concentrations in Patients with Chronic Renal Failure*. Tohoku J. Exp. Med., 2005, **205** (3), 263-268 —— Pepsinogen, the precursors of pepsin, is classified into two subtypes: pepsinogen I (PG I) and pepsinogen II (PG II). Patients with impaired renal function are associated with elevated concentrations of serum pepsinogen. Contradictory results have been reported about the effect of dialysis on the serum pepsinogen levels, as the previous studies were conducted only in a particular period of dialysis. We therefore investigated the effect of continuous ambulatory peritoneal dialysis (CAPD) or hemodialysis on serum pepsinogen levels in patients with chronic renal failure (CRF) before and after dialysis treatment. Thirty-four patients with CRF were enrolled in this study and were treated by CAPD (n = 22) or hemodialysis (n = 12). As a control group, subjects with normal renal function were included (n = 20). Serum PG I and PG II levels were measured in control subjects and CRF patients before dialysis treatment and after three-month dialysis treatment. Before dialysis treatment, serum PG I levels were significantly higher in CRF patients than control subjects. In patients treated by CAPD, the serum PG I levels were significantly decreased but its levels were still higher than the values of the control subjects, whereas PG I levels remained unchanged in patients treated by hemodialysis. There were no differences in serum PG II levels between control subjects and CRF patients before or after dialysis treatment. Thus, CAPD is more effective than hemodialysis in the clearance of PG I. ———— chronic renal failure; pepsinogen; continuous ambulatory peritoneal dialysis; hemodialysis

Pepsinogen (PG), the precursors of pepsin, originating from the stomach mucosa, is classified into two immunohistochemically distinguishable subtypes. These are pepsinogen I (PG I) and pepsinogen II (PG II) (Nakahama et al. 1995; Gritti et al. 2000). While PG I is released from the chief

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cells and the mucous cells in the fundus and corpus of the stomach, PG II is released from the pyloric glands in the antrum in addition to release sites of PG I. Changes in various patterns can be seen in the serum PG I and PG II levels in gastric pathologies (Axelsson 1992; Biemond et al. 1993). PGs are reported to be promising markers in serological diagnosis of some gastric disorders. However, the currently accumulated data are mainly those of the patients without apparent renal disease (Samloff et al. 1982; Nakahama et al. 1995; Yoshihara et al. 1998).

In patients with chronic renal failure (CRF), gastrointestinal system (GIS) symptoms and gastroduodenal lesions are frequently observed (Mitchell et al. 1979; Milito et al. 1983; Kang 1993). The factors responsible for such complications include the changes in the GIS hormone levels in CRF (Owyang et al. 1979; Taylor et al. 1980; Sirinek et al. 1984; Nakahama et al. 1995).

Many investigators reported changes in serum PG levels in patients with CRF treated by hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD). Contradictory results are available from the studies examining the effect of dialysis on PG levels (Swamy et al. 1981; Nakahama et al. 1995; Araki et al. 1999; Tamura et al. 1999). The main reasons for this confusion include a small number of patients, different renal replacement therapies used, and different stages of renal failure. Because the studies investigating the serum PG levels in CRF patients were conducted mainly in a particular period of the renal replacement therapy, the changes caused by dialysis could not be fully demonstrated. In this study, we investigated the effect of CAPD and HD treatment on serum PG levels in CRF patients who were diagnosed for the first time.

Subjects and Methods

Thirty-four consecutive patients (14 male, 20 female), who were diagnosed in our center as having CRF for the first time between November 2002 and December 2003, were included in the study. The twenty-two (nine male, 13 female) of 34 patients were treated by CAPD, and 12 (five male, seven female) of 34 patients were treated by HD. Twenty (11 male, 9 female) subjects with normal renal function who has appropriate age and gender were enrolled as a control group. This study was conducted by getting permission from the ethic committee of the Zonguldak Karaelmas University School of Medicine.

The patients who had prior stomach surgery, who had taken eradication treatment for *Helicobacter pylori* (*H. pylori*), 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.

Serum PG I and PG II levels and biochemical parameters were measured in control subjects and CRF patients before dialysis treatment and after three-month dialysis treatment. Blood samples were taken from superficial vein of the forearm. In patients treated by HD, the blood samples were taken 30 min before each HD. 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. The biochemical parameters were measured in our central laboratory using routine automated technic. The fasting serum PG I and PG II levels were measured by radioimmunoassay (Dainabot, Tokyo). The normal ranges with this test kit are 20-100 pg / ml for serum PG I, and 5-40 pg / ml for serum PG II. Residual renal function was estimated from the glomerular filtration rate (GFR) as calculated from the mean of urea and creatinine clearances (van Olden et al. 1996).

Hemodialysis with bicarbonate was administered for 4 hours 3 times a week by using Hollow-Fiber dialysers with polysulphane membrane and 1.2 m^2 of surface area to 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 35 kcal / kg / day energy, 1.2-1.4 g / kg / day protein, 1,000 mg / day calcium, 600 mg/day phosphorus, and 250 mg / day magnesium was administered.

Statistical analyses

In the CAPD and HD patients, paired *t*-test was used for the comparisons of the values before and after dialysis treatment. In the comparison between the CAPD, HD, and control groups the ANOVA or Kruskal Wallis analysis was used. When differences were detected in these analyses, the Tukey test or the Bonferonni-corrected Mann Whitney's U-test was used to demonstrate the differences between the groups. Statistical analysis was performed using SPSS (Statistical Package

for the Social Sciences) software.

Results

The demographic characteristics and the CRF etiologies of the patients are shown in Table 1. The biochemical parameters include the blood urea nitrogen (BUN), serum creatinine, serum PG I and PG II levels, GFR, and PG I / PG II ratio in control subjects and CRF patients before treatment and after three-month treatment (Table 2). Before treatment, serum PG I levels were significantly higher in CRF patients than control subjects ($p < 0.01$). In patients treated by CAPD, the serum PG I levels were significantly decreased ($p < 0.05$) but its levels were still higher than the values of the control subjects ($p < 0.01$), whereas PG I levels remained unchanged in patients treated by HD ($p > 0.05$).

Table 1. *Demographic characteristics and primary diseases of the patients*

	CAPD ($n = 22$)	HD ($n = 12$)	Control ($n = 20$)
Age (Years)	41 ± 8	44 ± 8	43 ± 7
Gender (F / M)	13 / 9	7 / 5	9 / 11
Primary disease			
Diabetic nephropathy	8	4	
Chronic glomerulonephritis	5	2	
Hypertensive nephropathy	5	1	
Chronic pyelonephritis	-	1	
Obstructive nephropathy	3	2	
Polycystic renal disease	-	1	
Amyloidosis	-	1	
Etiology is not known	1	-	

Table 2. *The mean serum levels of PG I and PG II and PG I / PG II ratio of the individuals*

	CAPD ($n = 22$)	HD ($n = 12$)	Control ($n = 20$)	p value
BUN before treatment (mg / 100 ml)	64.5 ± 17.4	68.3 ± 14.8	11.8 ± 3.6	NS[a], < 0.001[b,c]
BUN after treatment (mg / 100 ml)	57.4 ± 13.5	62.1 ± 12.3		NS[a]
Creatinine before treatment (mg / 100 ml)	8.5 ± 3.1	8.2 ± 3.1	0.6 ± 0.3	NS[a], < 0.001[b,c]
Creatinine after treatment (mg / 100 ml)	6.2 ± 1.8	7.4 ± 2.5		NS[a]
GFR before treatment (ml / min)	8.1 ± 5.5	8.4 ± 4.5	108 ± 19	NS[a], < 0.001[b,c]
GFR after treatment (ml / min)	6.3 ± 3.6	3.3 ± 2.9		< 0.05[a]
PG I before treatment (pg / ml)	266.8 ± 62.4	253.5 ± 63.4	108.2 ± 35.6	NS[a], < 0.01[b,c]
PG I after treatment (pg / ml)	211.6 ± 43.8	271.3 ± 58.2		< 0.05[a]
PG II before treatment (pg / ml)	24.2 ± 9.3	22.8 ± 8.4	22.3 ± 9.6	NS[a,b,c]
PG II after treatment (pg / ml)	21.6 ± 6.8	20.3 ± 5.9		NS[a]
PG I / PG II before treatment	11.1 ± 3.1	12.6 ± 3.8	5.4 ± 2.5	NS[a], < 0.01[b,c]
PG I / PG II after treatment	8.1 ± 2.8	15.4 ± 6.4		< 0.01[a]

NS, not significant. [a]continuous ambulatory peritoneal dialysis vs hemodialysis.
[b]continuous ambulatory peritoneal dialysis vs control group.
[c]hemodialysis vs control group.

There were no differences in serum PG II levels between control subjects and CRF patients before or after dialysis treatment ($p > 0.05$). There was a slight decrease in the serum PG II levels after three-month treatment, but this decrease was not statistically significant ($p > 0.05$).

Before treatment, PG I / PG II ratio was significantly higher in CRF patients than control subjects ($p < 0.01$). In patients treated by CAPD, the PG I / PG II ratio showed a decrease, which is proportional to the reduction in the serum PG I levels, but the ratio was still higher than control subjects ($p < 0.01$). In patients treated by HD, the PG I / PG II ratio did not change significantly.

Helicobacter pylori infection was found positive in 17 (77%) of the 22 CAPD patients, in nine (75%) of the 12 HD patients, and in 15 of the 20 (75%) control subjects. There were no differences between the groups in regard of *H. pylori* positivity.

Discussion

The kidney plays the key role in the elimination of PG (ten Kate et al. 1988). Thus, the serum PG levels increase in patients whose renal functions are impaired. In previous studies, it was shown that serum PG levels increase proportionally with the increase in the creatinine levels and this increase also exists in patients treated by HD (Swamy et al. 1981; Paimela et al. 1985; Nakahama et al. 1995; Araki et al. 1999; Tamura et al. 1999). There are no adequate data about the effect of CAPD, used as a renal replacement treatment in CRF, on serum PG levels. In addition, the previous studies on this topic were conducted only in a certain period of CAPD and HD, and there are no comparisons with pre-dialysis values.

In this study we have shown that before dialysis treatment serum PG I levels are significantly higher in CRF patients than control subjects. In patients treated by CAPD, the serum PG I levels were significantly decreased, but its levels were still higher than the values of the control subjects, whereas the PG I levels remained unchanged in patients treated by HD. There were no differences in serum PG II levels between control subjects and CRF patients before or after dialysis treatment.

Our findings are in agreement with the previous reports, showing that serum PG I levels are increased in CRF and HD patients (Nakahama et al. 1995; Araki et al. 1999; Tamura et al. 1999). In contrast, different results have been reported on the serum PG II levels in CRF and HD patients (Nakahama et al. 1995; Araki et al. 1999; Tamura et al. 1999); the serum PG II levels were increased in patients treated by HD (Nakahama et al. 1995; Tamura et al. 1999), whereas the PG II levels did not change in patients treated by HD (Araki et al. 1999). The present study favors the latter observations.

There are few studies investigating the effect of CAPD on PG levels in CRF patients. Nakahama et al. (1995) reported that 21 CAPD patients had a significant increase in the serum PG I and PG II levels compared to the control subjects. Tamura et al. (1999) analyzed eight CAPD patients, but these patients had been treated by CAPD for a long time. Moreover, the serum PG levels of the patients before CAPD treatment were unknown in these previous studies.

The metabolic differences between PG I and PG II and the effects of dialysis on serum PG levels can explain the differences in PG levels in HD and CAPD patients (Samloff et al. 1970; ten Kate et al. 1988; Araki et al. 1999). In spite of similar molecular weights, the mean fractional excretion of PG I and PG II in the urine are 27.6% and 1%, respectively in healthy individuals. The reason of this is due to the difference in the tubular reabsorption rates (ten Kate et al. 1988). Low renal excretion of PG II may explain why its levels in our patients were not changed in CAPD and HD patients.

The renal residual functions are well preserved in patients treated by CAPD, as the mean GFR levels were significantly higher in patients treated by CAPD than those treated by HD. The lower levels of PG I in patients treated by CAPD may reflect more preserved residual renal functions and high peritoneal dialysis clearance.

Patients who are positive for *H. pylori* have significantly higher PG levels than patients negative for this organism. This possibly related to

gastric mucosal change. We investigated the prevalence of *H. pylori* and found no differences between the groups. In the majority of the studies investigating *H. pylori* prevalence in patients with CRF, no significant difference in the *H. pylori* frequency was detected between the patients with and without CRF (Fabrizi and Martin 2000). The prevalence of *H. pylori* is approximately 70% in Turkish population (Us and Hascelik 1998). In our study, we found that *H. pylori* prevalence in the CAPD, HD and control groups were 77%, 75% and 75%, respectively. There were no differences in the frequency of *H. pylori* positivity between the groups.

In summary, HD has no noticeable effect on the increased serum PG I levels in patients with CRF, whereas CAPD could reduce the PG I levels. The effect of uremia and dialysis treatment type on the mean PG II levels is not significant. The lower PG I levels in patients treated by CAPD may reflect well-preserved residual renal functions and high peritoneal dialysis clearance in CAPD. CAPD is more effective than HD in the clearance of PG I.

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