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Effect of Peritoneal Glucose Load on Plasma Leptin Concentration in Continuous Ambulatory Peritoneal Dialysis Patients

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Abstract

This study was performed to investigate the effect of peritoneal glucose load on plasma leptin concentrations in the continuous ambulatory peritoneal dialysis (CAPD) performed on 13 non-diabetic ESRD patients. Plasma leptin and insulin concentrations were measured for 2 hours during a single 2 liter exchange of 1.5% glucose-based dialysate (SPD, n=6), for 7 days of daily peritoneal dialysis (DPD, n=7). In DPD, standard full volume (2,000 ml×4 times/day) exchange was performed immediately after operation. In SPD, plasma leptin and insulin concentrations remained unchanged during the study. In DPD, the plasma leptin concentration increased significantly after CAPD on the first day (PD1) (11.2±5.4 to 17.0±6.0 ng/mL, $p<0.05$) and this elevation seemed to persist until 7 days after operation. After CAPD, there was no significant day-to-day variation in peritoneal glucose absorption (391−465 cal). Oral intake seemed to decrease on operation day (PD0) and PD1 and then increased slowly. Plasma insulin and glucose concentrations did not significantly change after CAPD. Changes of leptin concentration were significantly correlated with the changes of peritoneal glucose absorption at PD1. In conclusion, continuous peritoneal glucose load may affect plasma leptin concentrations in CAPD patients.

Key Words: Leptin, CAPD, glucose, Insulin

INTRODUCTION

The highest elevation of plasma leptin level is reported to date among patients with terminal renal failure undergoing regular peritoneal and hemodialysis treatment.[1] CAPD patients seem to have significantly higher serum leptin levels than HD patients.[2] Hyperleptinemia in CAPD patients mainly results from the loss of renal elimination capacity combined with increased production due to obesity.[3,4] A strong correlation has been documented between the increase in serum leptin level and the body fat content, and it is likely that an increase in body fat mass is the single most important cause of increased serum leptin levels during PD.[5] Because the kidneys play an important role in the catabolism of insulin[6] and because insulin resistance is a well recognized feature of chronic renal failure,[7] prolonged biological action of insulin in patients with ESRD could well be a contributory mechanism for hyperleptinemia.[8,9] Indeed, a significant correlation has been observed between serum leptin and insulin concentrations in CAPD patients.[10]

However, factors other than reduced renal clearance of leptin, obesity and hyperinsulinemia may also contribute to hyperleptinemia in CAPD. Fontan et al.[2] showed that hyperleptinemia in CAPD patients may only partly be explained by the differences in gender distribution, fat mass, and insulin levels. They concluded that other factors, although undefined, may also have a role in the genesis of hyperleptinemia. Kim et al.[11] also showed that serum leptin concentration did not decrease during a 5 day period following the start of PD, despite its removal by PD, but that its concentration did increase markedly thereafter, within 3 months of the start of PD. They could not find a significant correlation between the change in leptin concentration and the change in BMI. They concluded that factors other than fat-mass gain can stimulate an increase in leptin concentration shortly after the start of PD.

Much evidence suggests that leptin is involved in the energy balance in humans. Congenital leptin

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deficiency in humans leads to hyperphagia and marked obesity.[12] Fasting or energy restriction decreases leptin concentrations acutely and disproportionately relative to the modest changes in adiposity.[13-16] The decrease in circulating leptin concentrations during energy restriction in humans is related closely to the decrease in plasma glucose level.[14] The infusion of amounts of glucose sufficiently small enough to prevent a decrease in glycemia and insulinemia during fasting in humans also prevents a decrease in plasma leptin level.[16] In addition, Mueller et al reported that glucose uptake and utilization are important determinants of leptin expression and secretion from isolated adipocytes.[17] Grinspoon et al.[18] reported that leptin concentrations increased significantly within 24 hours of glucose infusion. Insulin might mediate the effect of caloric intake on leptin level and could be a determinant of its plasma concentrations.

These results lead to the hypothesis that the peritoneal glucose absorption during CAPD induces hyperleptinemia.[19] Glucose is the principle osmotic agent in CAPD. Continuous glucose load during CAPD seemed to result in chronic hyperinsulinemia,[20] which is of interest because insulin has been shown to regulate leptin mRNA. Therefore, we performed this study to investigate the effect of peritoneal glucose load on plasma leptin concentrations in CAPD patients.

MATERIALS AND METHODS

Subjects

We investigated the effects of single peritoneal dialysis (SPD) and daily PD (DPD) on plasma leptin concentrations. Table 1 shows subject characteristics. The SPD regime included 6 non-diabetic clinically stable ESRD patients who had been on CAPD for more than 6 months. The mean age was 52±13 years, duration of CAPD was 38.3±27.3 months (12−61 months), and body mass index (BMI) was 18±3 kg/m^2. The male to female (M : F) ratio was 1 : 2. The DPD regime included 7 non-diabetic clinically stable ESRD patients who initiated CAPD. The mean age was 59±16 years, BMI was 19±2 kg/m^2 and M : F ratio was 1 : 1.1. Patients were excluded if they had edema severe enough to require a higher percentage of glucose dialysate.

Table 1. Patients Characteristics

	SPD	DPD
N	6	7
Age (years)	52±13	59±16
BMI (kg/m^2)	18±3	19±2
M : F	1 : 2	1 : 1.1

N, number; BMI, body mass index.

Methods

SPD was performed at noon before the meal. Plasma leptin and insulin levels were measured before dialysis and 30 mins, 1 hour, and 2 hours after dialysis with 1.5% 2,000 ml dialysate (Dianeal®, Baxter Healthcare Corporation, McGaw Park, Illinois, USA). To investigate the effect of DPD on plasma leptin concentrations, plasma leptin, insulin, and glucose concentrations were measured before (PD-1) and 1 (PD1), 3 (PD3), and 7 (PD7) days after CAPD. In DPD, CAPD exchanges were performed with immediate full volume (2,000 ml×4 times/day) beginning from the operation day (PD0). Plasma samples were obtained before oral intake every morning at same time (at 6 AM).

Plasma leptin concentrations were determined in specimens by RIA kit (Linco Research, St Charles, MO, USA). Plasma insulin levels were determined by RIA kit (Bio-source Europe, Fleurus, Belgium). A regular diet was offered by a dietitian (1,000−1,500 cal/day). The calorific value of unconsumed food was estimated and subtracted from the daily diet calories.

Calories derived from peritoneal glucose absorption were calculated using the method introduced by Davies et al.[21] Each patient underwent a standard peritoneal equilibration test.[22] This provides an accurate and repeatable assessment of the peritoneal fractional absorption of glucose, which is independent of the concentration of glucose instilled in the peritoneum.[23,24] In SPD, the PET data from the previous 3 month period was used. In DPD, PET was performed 4 days after operation. The total glucose absorption over 24 hours was calculated as the product of fractional glucose absorption, the number of exchanges, and the volume and concentration of glucose used in the dialysis regime. It was assumed

that the overnight value for the fractional glucose absorption was 1.0, in order to allow for further equilibration during the longer dwell period. The glucose absorption was converted into calories.

Glucose absorbed (g)=n×Vin×10×% glucose×D/D0 glucose

where n=number of exchanges

Vin=volume of instilled dialysate

% glucose=percent of glucose in dialysate (g/dl)

D/D0 glucose=fractional absorption of glucose

Calories=Glucose absorbed from peritoneum (g)×4.18.

Statistical analysis

Results were expressed as mean±SEM and analyzed using the Wilcoxon signed ranks test. Spearmans correlations were used to assess the relationship between changes of plasma leptin level and changes of other variable. $P<0.05$ was accepted as significant.

RESULTS

Effect of SPD on plasma leptin concentration

Basal plasma leptin concentration was 16.0±11.1 ng/ml. Leptin concentrations at 30 minutes, 1 hour and 2 hours were 18.1±13.6, 18.9±14.4, 16.3±11.5 ng/ml (Fig. 1). Basal plasma insulin level was 8.3±2.3 μU/ml. Insulin levels at 30 minutes, 1 hour and 2 hours were 11.0±2.6, 16.2±6.9, 10.1±3.1 μU/ml (Fig. 2). Plasma leptin and insulin concentrations remained unchanged during the study.

Effect of DPD on plasma leptin concentration

Baseline plasma leptin concentration before CAPD operation (PD-1) was 11.2±5.4 ng/ml. Leptin concentration at PD1 (17.0±6.0 ng/ml) was significantly elevated ($p<0.05$), and tended to remain elevated at the third day after CAPD operation (PD3) (19.9±5.3 ng/ml) and the seventh day after operation (PD7)

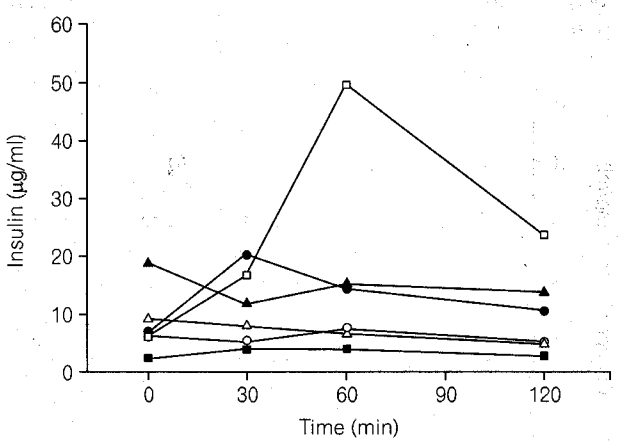

Fig. 2. Changes in plasma insulin concentrations in SPD. SPD: single peritoneal dialysis with 1.5% 2 liter glucose-based dialysate.

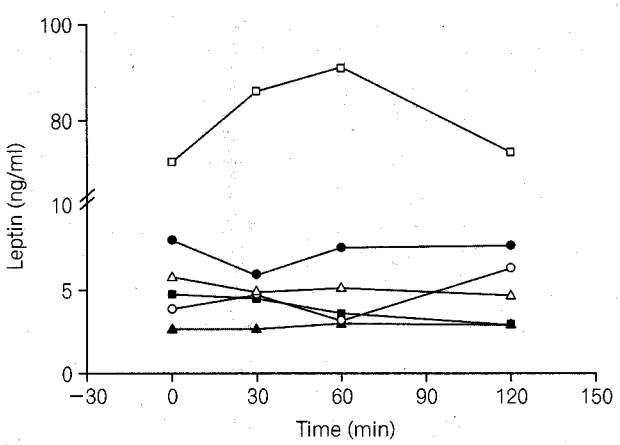

Fig. 1. Changes in plasma leptin concentration in SPD. SPD: single peritoneal dialysis with 1.5% 2 liter glucose-based dialysate.

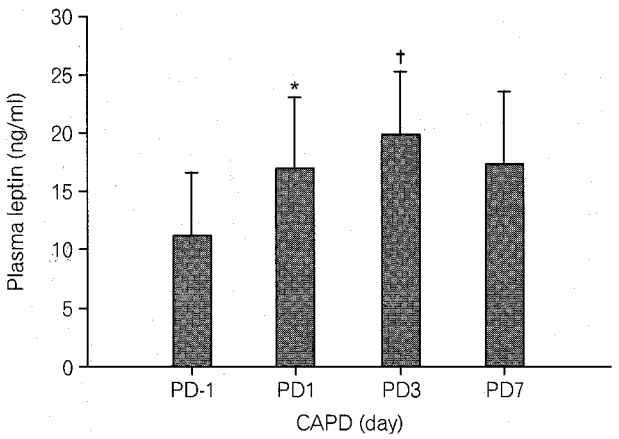

*Fig. 3. Changes in plasma leptin concentrations in DPD. DPD: daily peritoneal dialysis with standard 2 liter 4 exchange regime. *$p<0.05$ vs. PD-1, †$P=0.06$ vs. PD-1, Error bar means SEM.*

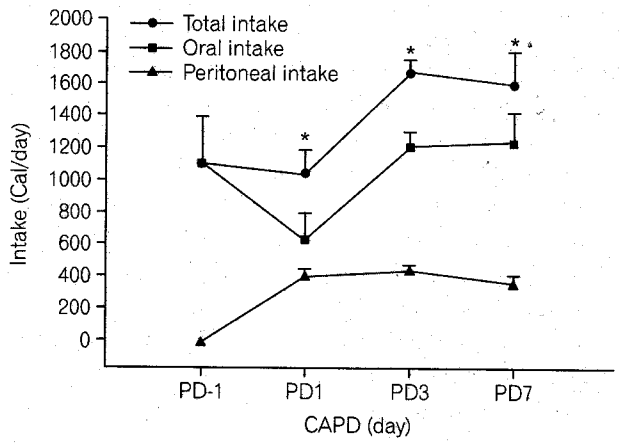

*Fig. 4. Changes in total, oral, and peritoneal intake in DPD. DPD: daily peritoneal dialysis with standard 2 liter 4 exchange regime. *p <0.05 vs. oral intake on the same day. Error bar means SEM.*

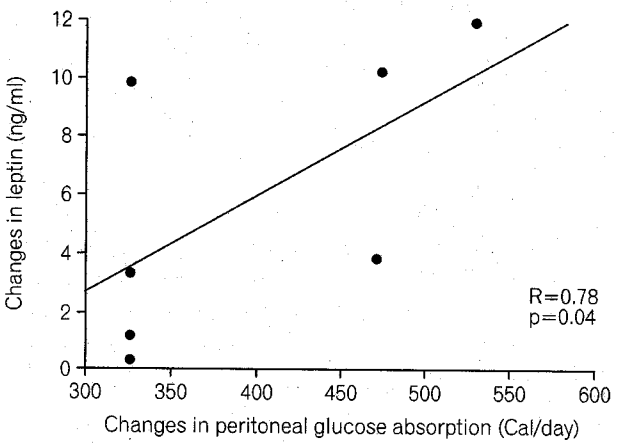

Fig. 5. Correlation between the changes in plasma leptin and the changes in peritoneal glucose absorption at PD1 in DPD. DPD: daily peritoneal dialysis with standard 2 liter 4 exchange regime.

(17.3±6.2 ng/ml) (Fig. 3). After CAPD, total intakes were significantly more increased than the oral intakes at PD1, PD3, and PD7 (Fig. 4). These increments were mainly caused by peritoneal glucose absorption. The oral intake seemed to decrease at PD1, and then increased slowly (881.4±387.6, 630.0±428.3, 1201.4 ±238.1 and 1131.4±302.3 cal/day at PD0, PD1, PD3, and PD7). The amount of daily peritoneal glucose absorption was constant during the 7 days (391.86±21.7, 412.20±19.5, 465.55±65.7, 394.01 ±19.4 calories at PD0, PD1, PD3, and PD7). The changes in plasma leptin level after CAPD were similar to those of peritoneal intake (Fig. 3 and 4). At PD1, the changes in leptin concentration were

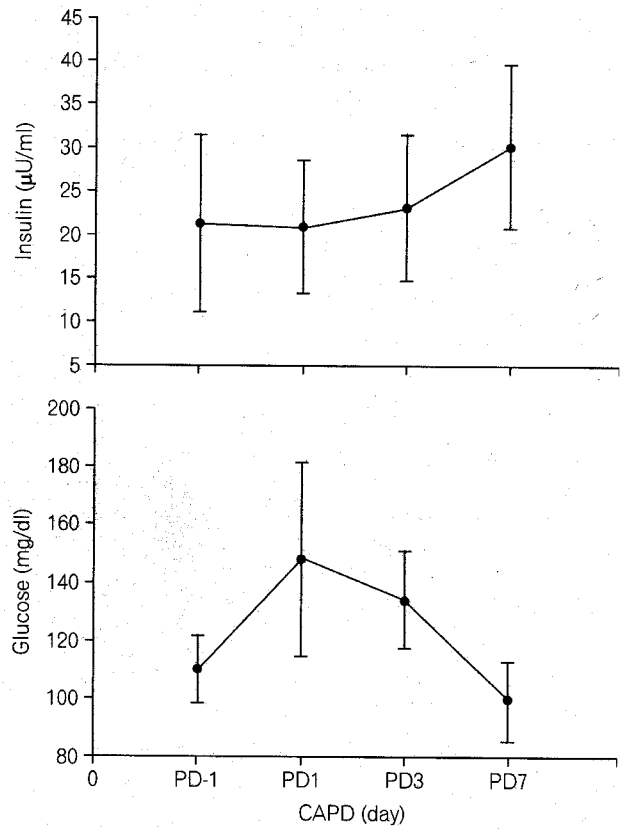

Fig. 6. Changes in plasma insulin and glucose concentrations in DPD. DPD: daily peritoneal dialysis with standard 2 liter 4 exchange regime.

significantly correlated with the changes in peritoneal glucose absorption (r=0.78, p=0.038) (Fig. 5). Plasma insulin and glucose concentrations showed a few fluctuations after CAPD without statistical significance (Fig. 6). No significant association was observed between leptin concentration and dietary calorie intake, insulin, or BMI.

DISCUSSION

A novel finding from the present study is that SPD does not significantly affect plasma leptin levels, but that DPD can affect them. Circulating leptin levels were significantly increased after CAPD and this elevation seemed to persist for several days in DPD. Furthermore, the leptin levels were elevated in spite of the decrease in oral intake and the changes in leptin concentration were significantly correlated with the changes in peritoneal glucose absorption at PD1.

Our results suggest that continuous peritoneal glucose load may induce hyperleptinemia in CAPD patients. Kim et al.[11] also studied the changes in leptin concentration after CAPD operation. They found that serum leptin concentration did not decrease during the 5 day period after the start of CAPD despite its removal by PD and that it increased markedly thereafter, during the 3 month period after the start of PD.

A continuous glucose load during CAPD results in chronic hyperinsulinemia.[20] It has been shown that long-term (72 hour), but not acute, insulin infusion stimulates leptin secretion.[8,9,25] In this study, we could not find evidence of the elevation of glucose and insulin concentrations after DPD. How can we explain the elevation of plasma leptin concentration from 1 day after CAPD operation in spite of relatively stable plasma insulin and glucose concentrations after CAPD? CAPD dose not always elevate plasma insulin concentration. Lindholm and Karlander[26] reported that blood glucose and serum insulin levels were not significantly different in fasting patients from those of healthy controls. Armstrong et al.[27] reported that when employing the 1.5% solution, plasma glucose level remained stable and only a slight insulin stimulation was observed. Only in the case of the 4.25% solution did plasma glucose levels rise above 100 mg/dl. Four of the 5 patients responded to this change with marked insulin secretion. During SPD, blood glucose and insulin levels rose during dialysis, particularly with hypertonic dialysate and the levels remained high for 6 h after the onset.[28] Considering this background, our results may be due to the predominant use of 1.5% solution. Our subjects also did not have edema severe enough to require hypertonic dialysate. In addition, the SPD subjects had been on CAPD for more than 6 months. Therefore, they may have developed the ability to adapt to the peritoneal glucose load. However, the DPD subjects had never been exposed to PD. Also, we performed standard 2,000 ml 4 exchange PD regime after operation. This may considerably affect the results of our study.

On the other hand, plasma insulin concentration may not be an accurate measure of pancreatic beta-cell stimulation in CAPD patients.[20] Furthermore, native insulin can be transferred through the peritoneal membrane during CAPD.[29] Therefore, the lack of change in plasma insulin levels during DPD may be partly explained by these previous results.

Recently, it has been shown that physiological insulinemia can regulate plasma leptin level.[30] In a reported vivo study,[31] a positive energy balance, caused by overfeeding, resulted in a significantly higher amplitude of the 24 h plasma leptin curve. These effects were not acute, but were manifest within 24 hours. Continuous peritoneal glucose absorption by the use of 1.5% solution may also induce a slight insulin stimulation, which may regulate plasma leptin concentration.

Another possible cause of an increase in plasma leptin level is that a the continuous absorption of glucose from the peritoneal dialysate may stimulate leptin production by an insulin-independent mechanism.[32] Or finally, the increased generation of pro-inflammatory cytokines may also be a factor stimulating leptin gene expression.[4,33] It is possible that the CAPD operation itself may stimulate proinflammatory cytokines. However, C-reactive protein remained stable during the DPD study (data not shown), and prophylactic antibiotics and meticulous wound care were employed.

This study has several limitations. The use of 4.25% solution may induce more definite results than 1.5%. Also, the number of subjects was too small. However, this pilot study suggests that the undefined other factor causing hyperleptinemia in CAPD patients may be continuous peritoneal glucose load.

In conclusion, we found that DPD, not SPD, could increase circulating leptin concentrations. Thus, continuous peritoneal glucose load by CAPD may regulate plasma leptin concentrations but further investigations with a greater number of patients are required to clarify this issue.

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