
Case Report

Impact of long-term home parenteral nutrition on bone metabolism and mineral density: a case report

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ABSTRACT: Objective: To analyze the impact of home parenteral nutrition (HPN) on bone metabolism and bone mineral density (BMD).

Methods: The biochemical markers bone metabolism and BMD (with dual-energy x-ray absorptiometry) were assessed before starting HPN and during 42 months of follow-up in a patient with intestinal pseudo-obstruction who apparently had no other factors interfering with bone metabolism.

Results: Before starting HPN, a hyperkinetic bone turnover and a negative calcium balance were present, and BMD T-score (standard deviations below mean BMD of healthy young subjects) was -3.9 at spine and -2.9 at femur. During the follow-up, bone turnover normalized and BMD significantly decreased at femoral neck and remained stable at spine. Regression analysis showed that duration of HPN was associated negatively with serum osteocalcin and urinary pyridinolines, and with serum parathyroid hormone (PTH).

Conclusions: The results agree with the hypothesis of the development of a low bone turnover and a decreased bone sensitivity to the PTH bone-building action during long-term HPN. (*Nutritional Therapy & Metabolism* 2008; 26: 86-92)

KEY WORDS: Bone metabolism, Bone mineral density, Bone turnover, Long-term home parenteral nutrition, Serum parathyroid hormone

INTRODUCTION

Patients on long-term home parenteral nutrition (HPN) may develop a metabolic bone disease characterized by asymptomatic osteopenia, bone pain localized mainly at lower joints, or by bone fractures which occur with no or minimal trauma (1-3). The pathogenesis of the disease is multifactorial and not yet completely understood. Cross-sectional and follow-up studies in healthy subjects or in patients on HPN showed that parenteral formula composition and schedule may interfere with calcium metabolism (1-3). However, the presence of factors due to the underlying disease playing a role in the pathogenesis of bone disease (inflammation, drugs, etc.) often interfere with investigation of the impact of long-term HPN on bone metabolism and mineral content of patients with chronic intestinal failure (1-3). An optimal study model would require the observation of healthy subjects receiving long-term total parenteral nutrition or of patients in whom HPN is the only variable, while no factors related to the underlying disease are present and oral food and physical activity are sta-

ble. Recently, we put a woman affected by chronic idiopathic intestinal pseudo-obstruction (CIPO) (4) on HPN. She tolerated only small amounts of an elemental diet and apparently had no other factors interfering with bone metabolism. This condition was considered to be of special interest for the observation of the impact of long-term HPN on bone metabolism and bone mineral density (BMD). The results of a 42-month follow-up study are reported.

METHODS

HPN was started in a 55-year-old white woman (physiologic menopause at age 50 years), affected by CIPO. She complained of chronic constipation (< 1 bowel movement/week) since adolescence and underwent a cholecystectomy when she was 34 years old. The diagnosis of CIPO was made when she was hospitalized for an acute abdominal distension associated with diffuse abdominal pain. Barium enema revealed the presence of megacolon. In the contrast, anorectal manome-

try showed the presence of a normal rectoanal inhibitory reflex, excluding Hirschsprung's disease. The evaluation of intestinal transit time showed a prolonged stay of the radiolabeled capsule in sigmoid and rectum (> 200 and > 300 hours, respectively). Colonic endoscopy did not show any abnormalities, and rectal biopsies were normal. Small intestine manometry showed abnormal migrating motor complex (MMC) regarding both propagation and morphology (i.e., altered tonic and phasic activity or uncoordinated bursts). The patient started medical treatment with prokinetic drugs and low-fiber diet, which was replaced some years later with a liquid diet. Due to the increased frequency of the occlusive episodes, the tolerance to enteral feeding further decreased, the patient lost about 10% the usual body weight, and the decision to start a HPN program was taken.

HPN regimen

Parenteral solution was administered overnight as cyclical infusion. The basic solution consisted of hypertonic dextrose and standard crystalline amino acid formula with addition of electrolytes. Calcium was provided as calcium chloride. When prescribed, intravenous soybean-based fat emulsion was added to the solution by the patient, just before the beginning of the infusion. Three milliliters of a mixed trace metal solution (zinc, 1 mg/mL; copper, 0.4 mg/mL; manganese, 0.1 mg/mL, chromium, 0.004 mg/mL) and 1.02 mol of selenium were routinely added to the nutrient solution. Vitamins were added to each infusion in the form of Cernevit, which contains 200 IU vitamin D (cholecalciferol) and 3,500 IU vitamin A (retinol).

Follow up protocol

According to our protocol, the patient was assessed the day before (baseline at 3 days before HPN) the central venous catheter positioning and after 1, 4, 6, 12, 18, 24, 30, 33, 36, and 42 months of HPN. The following parameters were measured: body weight (BW); rehabilitation status; serum osteocalcin (OC) as marker of bone formation, intact parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (1,25(OH)₂-D); fasting urinary hydroxylysyl pyridinoline (HP) and lysyl pyridinoline (LP) as markers of bone resorption; serum concentration (S) and 24-hour urinary excretion (U) of calcium (Ca), phosphorus (P) and magnesium (Mg); glomerular filtration rate (creatinine clearance); serum albumin; serum aluminum (Al); bone mineral density (BMD); erythrocyte sedimentation rate (ESR, first hour normal value < 20), and serum C-reactive protein (CRP, normal value < 0.6 mg/dL). Between the assessments, the oral

intake, the HPN composition and schedule, and the medications taken by the patient were recorded.

From the body weight and the height of the patient the body mass index (BMI) was calculated by Quetelet's formula (kg/m²; normal values: 18.5-25). The rehabilitation status was assessed according to Mughal and Irving (5): grade 1, at work full-time or looking after home and family unaided; grade 2, at work part-time and/or looking after home and family with help; grade 3, unable to work but able to cope with HPN unaided and to go out occasionally; and grade 4, house-bound, needing major assistance with HPN.

Serum and urinary chemistries

Blood samples were drawn between 7:00 AM and 9:00 AM, 2 to 3 hours after the end of the overnight HPN. PTH, OC, and vitamin D were analyzed by commercial radioimmunoassay: intact PTH (Nichols Institute, San Juan Capistrano, CA, USA), osteocalcin (CIS Bio International, Gif Sur Yvette, France), and 1,25-hydroxyvitamin D (Incstar Co, Stillwater, MN, USA). Reference normal ranges for OC were obtained from 27 healthy subjects (11 men, aged 35-57 years; 16 women, aged 34-66 years). Reference normal ranges for PTH and 1,25-hydroxyvitamin D were those from the RIA kits. Total HP and LP were measured in second spot urine samples collected in the morning in the fasting state and analyzed by high-performance liquid chromatography (HPLC) as previously described (6). Cross-links were expressed as pmol/μmol of creatinine. Urinary creatinine was measured in the same samples by automated techniques. Serum and urinary minerals were analyzed by colorimetric methods. Age- and sex-adjusted reference values for HP and LP were obtained from 48 healthy men and 48 healthy women. Serum aluminum was measured using graphite furnace atomic absorption spectrophotometry. In a group of 21 healthy adult subjects, serum aluminum concentrations ranged from 0.02 to 0.80 μmol/L (mean ± standard deviation: 0.35 ± 0.17 μmol/L). The mean + 2 standard deviations was considered the upper normal limit (0.69 μmol/L). Serum CRP was evaluated by nephelometry.

Bone mineral density

BMD was assessed by dual-energy x-ray absorptiometry (DEXA) at lumbar spine (L₁-L₄) and at femoral neck (densitometer: Norland XR36; Norland Co, Fort Atkinson, WI, USA). All of the BMD assessments were performed by the same technician. In our laboratory, the in vivo precision (coefficient of variation [CV] in 15 adult healthy subjects) was within 1.1% for lumbar

spine and within 1.6% for femoral neck. According to the CV, the minimal significant difference to be detected between 2 measurements performed in a single individual, calculated by the formula $(2 \cdot \sqrt{2} \cdot CV) \cdot (\%)$, is 3.1% at lumbar spine and 4.5% at femoral neck. The results are presented as g/cm² and as number of standard deviations below mean BMD of healthy young subjects (T-score).

Statistics

The relationships between the variables were examined by simple regression analysis.

RESULTS

Outcome

Before starting HPN (baseline) both OC and pyridinoline were higher than normal, S-Ca and S-Mg were low and a mild hypercalciuria was present (Tab. I). BMD T-score was -3.9 at spine and -2.9 at femur. BMI was 21.8, and serum albumin concentration was low normal. The rehabilitation status was grade 1. ESR and CRP were within the normal values. The daily oral intake was of 1,000 mL of elemental diet containing 11.5

mmol of Ca (recommended dietary allowance for Italian postmenopausal women: 30 mmol/day) (Tab. II).

Between the time before and after 6 months of HPN, OC remained elevated, pyridinoline normalized, and urinary calcium excretion slightly increased. BMD increased (+7%) at both sites. BMI and serum albumin increased. Rehabilitation status was stable. The inflammatory indexes remained negative. In the days of HPN infusion, the oral intake consisted of 8 tablespoons of sucrose and 100 g of maltodextrins diluted in about 2,000 mL of tea. On the days off HPN, the patient drank 500 mL of elemental diet and 2,000 mL of tea with 8 tablespoons of sucrose and 200 g of maltodextrins.

Between 6 and 42 months of HPN, OC normalized, pyridinoline remained normal, and calciuria further increased. BMD at femoral neck decreased significantly between 6 and 12 months (-7.4%) and between 12 and 30 months (-5%) and was stable between 30 and 42 months. BMD at lumbar spine did not show significant variations. Rehabilitation status was stable. The inflammatory indexes remained negative. On the day off HPN, the intake of elemental diet decreased to 250 mL/day. The intake of sucrose and maltodextrins was unchanged.

During the study period, the patient had no episodes of intestinal occlusion, did not take medications interfering with bone metabolism, and suffered no catheter-related

TABLE I - BIOCHEMICAL MARKERS OF BONE TURNOVER AND BONE MINERAL DENSITY

Follow-up	Serum concentration							Urinary		Urinary output			BMD	
	OC	PTH	Ca	P	Mg	Al	1-25 vit D	HP	LP	Ca	P	Mg	Spine L ₁ -L ₄	Femoral neck
(Months of HPN)	(pg/L)	(pmol/L)	(mmol/L)	(mmol/L)	(mmol/L)	(pmol/L)	(pmol/μmol creatinine)	(mmol/24 h)	(mmol/24 h)	(g/cm ²)	(g/cm ²)			
B	27	2.1	1.82	1.16	0.58	0.44		143	36	6.5	8.7	3.5	0.655	0.565
1	25	2.5	2.32	1.19	0.82		86	76	16	5.3	22.6	4.7		
4	35	1.9	2.27	1.10	0.74	1.29	72	96	23	7.9	29.0	6.3		
6	31	3.0	2.32	0.94	0.78	1.48	55	87	20	6.8	29.4	5.0	0.700	0.605
12	28	4.4	2.27	1.16	0.78	1.13		109	23	7.7	32.9	5.7	0.688	0.560
18	25	4.0	2.25	1.06	0.78			75	18	8.8	12.9	7.0		
24			2.15	1.13	0.82	0.63				12.8	23.2	10.0		
30	11	3.5	2.05	1.13	0.78	0.70	91	57	6	13.2	19.4	8.1	0.686	0.532
33	11	4.8	2.20	1.16	0.78	0.44	117	78	10	10.8	19.5	7.8		
36	11	4.2	2.17	1.13	0.82	0.25				10.8	30.4	10.2		
42	15	6.5	2.25	1.13	0.78			84	6	10.5	29.4	9.0	0.672	0.534
Reference value	5-14	1.0-7.3	2.12-2.75	0.64-1.61	0.75-1.20	< 0.69	38.4-100.8	56-136	8 - 32	1.25-6.25	12.9-35.5	2.08-6.16		

Al = aluminum; B = baseline at 3 days before starting HPN; BMD = bone mineral density; HP = hydroxylysyl pyridinoline; HPN = home parenteral nutrition; LP = lysyl pyridinoline; OC = osteocalcin; PTH = parathyroid hormone.

Fig. 1 - Relationships between the duration of home parenteral nutrition (HPN) and A) serum osteocalcin (OC), B) urinary lysyl pyridinoline (LP), and C) serum intact parathyroid hormone (PTH).

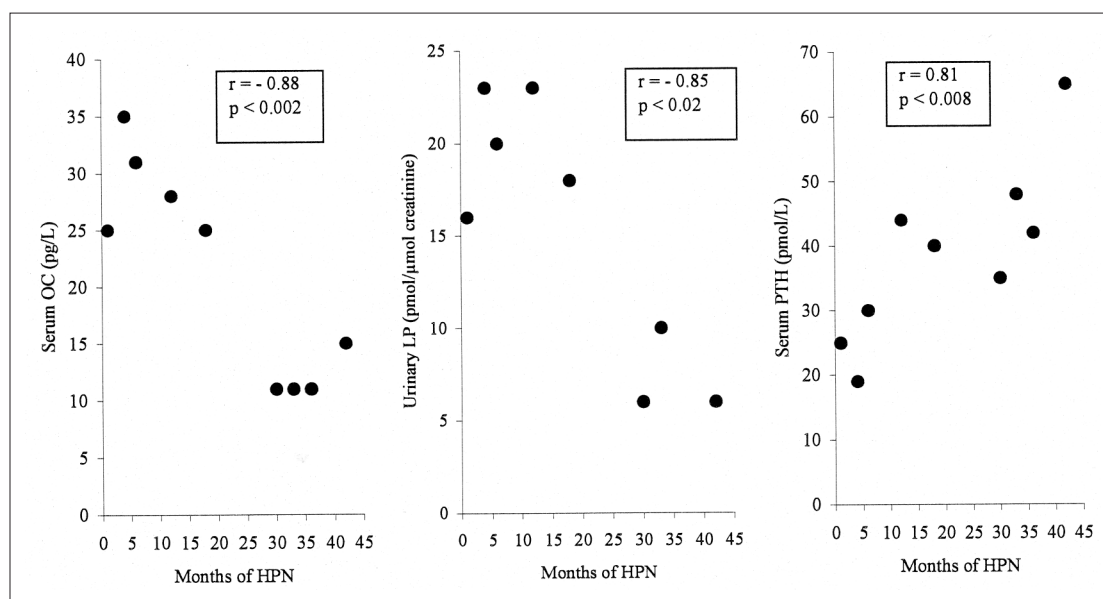


TABLE II - NUTRITIONAL STATUS, ENTERAL DIET AND HPN CHARACTERISTICS DURING THE FOLLOW UP

Follow-up	Nutritional status		Enteral diet	HPN characteristics								
	BW	Albumin		Schedule	Volume	AA	Glucose	Fat	Na	Ca	P	Mg
(Months of HPN)	(kg)	(g/L)	(mL/day)	(no./week)	(mL/day)	(g/day)	(g/day)	(g/day)	(mmol/day)	(mmol/day)	(mmol/day)	(mmo/day)
B	56	35.2	1,000									
1	56	43.4	500	4	2,000	68	240	0	100	5.4	24	4
4	58	39.9	500	4	2,000	68	240	0	100	5.4	24	4
6	59	40.2	250	4	2,000	68	240	0	100	5.4	24	4
12	59	41.9	250	5	2,500	85	300	0	124	6.8	30	5
18	59	39.3	250	5	2,000	85	180	50	124	8	15	8
24	59	39.7	250	5	2,000	85	180	50	124	8	15	8
30	59	46.0	250	5	2,000	85	180	50	124	8	15	8
33	59	40.1	250	5	2,000	85	180	50	124	8	24	8
36	59	41.9	250	5	2,000	85	180	50	124	8	24	8
42	59	39.2	250	5	2,000	85	180	50	124	8	24	8

AA = Amino Acids; B = 3 days before starting HPN; BW = body weight; HPN = home parenteral nutrition.

complications. Her physical activity did not change significantly, nor did her level of sun exposure, and she was a non-smoker. The glomerular filtration rate, measured at baseline, 12, 24, and 42 months, ranged from 76 to 80 mL/hour.

Simple regression analysis

The following associations were examined: serum OC vs. urinary LP ($r = 0.93$, $p < 0.002$) and urinary HP ($r = 0.65$, $p < 0.08$); duration of HPN vs. serum OC ($r = -0.88$, $p < 0.002$; Fig. 1A), urinary LP ($r = -0.85$, $p < 0.02$; Fig. 1B), urinary HP ($r = -0.38$) and serum

PTH ($r = 0.81$, $p < 0.008$, Fig. 1C); U Ca vs. P/Ca in HPN ($r = -0.60$, $p < 0.07$).

DISCUSSION

The results of this observational study agree with the hypothesis of the development of a low bone turnover and a decreased bone sensitivity to the PTH bone-building action during long-term HPN. Before starting HPN, there was a feature of hyperkinetic turnover associated with a low calcium intake and with

hypercalciuria, indicating a negative calcium balance. During the first 6 months of HPN, bone resorption normalized, bone formation remained elevated, and there was a consistent increase of BMD. The improvement occurred parallel to the increase in BW and serum albumin, suggesting that in underfed patients, nutritional support with HPN can also positively modify the calcium balance. After this first period, serum OC concentration and urinary pyridinoline excretion progressively decreased, and there was a significant decrease in BMD at femoral neck, while BMD at lumbar spine remained stable. Regression analysis showed a negative association between the duration of HPN and the markers of bone turnover. No factors interfering with bone metabolism other than HPN appeared to be present: menopause occurred 5 years before starting HPN, the underlying disease was stable, there were no signs of inflammation, no medications interfering with bone metabolism were given, and rehabilitation status was fair and stable. The patient oral intake was small and measurable and did not change after the first 4 months.

Our data are in keeping with the early observations indicating that during long-term HPN, bone turnover evolves at a low formation rate. Shike et al observed by bone histomorphometry a hyperkinetic bone turnover in the early months of HPN that turned to a low bone formation rate 1 year later (7). After this longitudinal study, all (8-13) but 1 (14) cross-sectional study reported the presence of a low bone formation rate in most patients on long-term HPN. Using serum biochemical markers of bone turnover, we observed results consistent with those reported with bone histomorphometry (6). The mechanism by which long-term HPN may cause a decrease in bone turnover is unclear. In the earliest studies (8, 9), aluminum toxicity due to the high aluminum content of casein hydrolysate accounted for the histomorphometric features observed. However, after the replacement of casein hydrolysate with crystalline amino acids, a low bone formation rate was observed despite no aluminum accumulation at the mineralization front of bone (11). As *in vitro* studies demonstrated that aluminum may inhibit the proliferation of osteoblasts (15, 16), it was hypothesized that chronic exposure to high serum aluminum without metal deposition in bone can also cause a decrease in bone formation. Another pathogenetic hypothesis is that of vitamin D toxicity due to the long-term intravenous administration of normal amounts of 25OH-D. It was firstly noted that a short-term withdrawal (10-14 months) of vitamin D consistently corrected the abnormalities observed in bone histology (17). The same authors showed that after a long-term withdrawal (> 4 years) of intravenous vitamin D (18), bone mineral content significantly in-

creased at lumbar spine, remained stable at femoral neck, and decreased at trochanter. Serum PTH and 1,25(OH)₂-D were low before vitamin D withdrawal and were normal at the end of the study. It was suggested that vitamin D toxicity may suppress PTH secretion and that the increased BMD observed after vitamin D withdrawal was due to the bone formation-stimulating effect exerted on the axial skeleton by the increased concentration of PTH. In the present study neither aluminum nor vitamin D toxicity seem to explain the progressive decrease in bone turnover, because serum aluminum was found to be higher than normal only during the first 12 months of HPN and both serum PTH and 1,25(OH)₂-D concentrations were always within the normal range.

The development of an altered response to PTH in patients on HPN has been previously suggested. In our patient there was a positive relation between the duration of HPN and serum PTH concentration. In a nonhuman primate model, PTH was higher in animals receiving intravenous nutrition than in those receiving oral diet. In the group receiving parenteral nutrition, calcium balance improved progressively with time due to the decrease in urinary calcium loss (19). The decrease in calciuria was inversely correlated with serum PTH concentrations, whereas calcium balance was directly associated with PTH. The author suggested that adaptations occur with time in parenteral nutrition therapy which result in calcium conservation and increased PTH concentration in blood. Our observation of a progressive increase of serum PTH agrees with this hypothesis, but we did not detect any parallel decrease in urinary calcium loss. This may be due to the fact that during the study period the phosphate and calcium content and ratio in the HPN formulation was changed, thus influencing the resorption of calcium by the renal tubules (20). Studies in animals and in humans demonstrated that PTH exerts a bone-building action by stimulating the generation of osteoblasts in the mature human skeleton (21). In postmenopausal women, exogenous PTH administration was associated with an increase of serum OC concentrations and an increase of BMD at spine (+10%-15%), whereas its effect at the femoral neck was limited (+2.4%) (21). This stimulating effect on bone formation exerted by PTH did not appear in our patient. Indeed, while serum PTH increased, serum OC concentrations decreased, and BMD remained stable at lumbar spine and declined at femoral neck.

Jeejeebhoy suggested that parenteral nutrition may modify the balance of the effect of PTH between resorption and formation in the direction of resorption, so that much higher concentrations of PTH are required to reduce resorption or promote bone formation (22). A

study on diurnal regulation of serum calcium and PTH concentrations during HPN showed that patients on long-term HPN had abnormal parathyroid gland function and mild secondary hyperparathyroidism (23). The nocturnal infusion of HPN solutions containing calcium disrupted the normal diurnal variations in serum calcium and PTH concentrations. The authors suggested that long-term HPN would increase the regularity of PTH secretion together with moderate but persistent elevations in serum PTH concentrations. These might lower the PTH/PTH-related peptide receptor expression and diminish the response to physiologic blood concentrations of PTH in target tissues. This would imply a reduced bone formation and turnover and a reduced renal calcium reabsorption (21, 22). A decreased sensitivity of bone to the effects of PTH could have developed in our patient. Thus, the increased serum concentrations of PTH were high enough to maintain lumbar spine BMD but not femoral neck BMD, which is less sensitive than vertebrae to the PTH bone formation activity.

Summarizing, this long-term observational study suggests that in the short-term, HPN may correct a pre-

vious impaired bone turnover and may increase BMD, whereas in the long-term, HPN may be associated with a decrease in bone formation and BMD. The long-term effect of HPN could be due to the development of a decreased sensitivity to the PTH bone-building action.

Conflict of Interest: none declared.

Patients' Informed Consent: not required because the study is an observational one, based on clinical data collected in the patients' record.

Financial support: none.

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Received: January 28, 2008

Accepted: May 6, 2008