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ORIGINAL ARTICLE

Bone mineral density in patients on home parenteral nutrition: a follow-up study

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Summary *Background & aims*: The variations of bone mineral density (BMD) during home parenteral nutrition (HPN) and their relationship with general, life style, primary disease and HPN risk factors were investigated by a follow-up study.

Design: Patients who had BMD assessment in a previous cross-sectional survey underwent a 2nd BMD at femoral neck (FN) and lumbar spine (LS). Data about risk factors were collected by a structured questionnaire. BMD *Z*-score (number of standard deviations from normal values corrected for sex and age) and the annualized percent BMD change were analysed.

Results: Sixty-five adult patients were enrolled (follow-up: 18.1 ± 5.5 months). The mean BMD *Z*-score significantly increased at the LS ($P = 0.040$) and remained unchanged at FN. In multiple regression analysis, the variations of the LS *Z*-score during HPN negatively correlated with the female sex ($P = 0.021$) and the age at starting HPN ($P = 0.022$). The analysis of the annualized percent BMD change confirmed the results obtained by the analysis of the *Z*-score. No factor was associated with BMD variation at FN.

Conclusions: HPN was not associated with a decrease of BMD in most of the patients; LS BMD *Z*-score variations were related to general risk factors rather than to HPN factors, showing a negative association with age and female sex.

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Introduction

Patients on long-term home parenteral nutrition (HPN) may develop a metabolic bone disease whose pathogenesis appears multifactorial.[1–5] The prevalence and the severity of bone disease in HPN for benign chronic intestinal failure have recently been evaluated by a cross-sectional multicentre study assessing the bone mineral density (BMD) in adult patients.[6] Bone disease was present in 84% of the patients according to the BMD *T*-score (the number of standard deviations from the mean BMD value of sex-matched healthy young adults) and in 62% according to the BMD *Z*-score (the number of standard deviations from the mean BMD value of sex and age-matched healthy controls); in one-half of the patients, the bone mineral density was of severe degree. Both the BMD *T*- and *Z*-scores appeared predictive of the risk of fracture. The prevalence of bone disease was similar between males and females, was greater in post-menopausal than in pre-menopausal women and did not differ between the primary gastrointestinal disease subgroups. The femoral neck (FN) BMD *Z*-score was positively associated with body mass index (BMI) and the lumbar spine (LS) BMD *Z*-score was positively associated with patient age at starting HPN. No factors directly due to HPN were found to be significantly related to the BMD *Z*-score.

A few follow-up studies[7–10] on variations of BMD during HPN were performed by single centres and included small patient groups. The results were not consistent among the various studies and the small number of patients hampered an extensive analysis of risk factors for loss of bone mass. In order to further analyse the variations of BMD during HPN for benign intestinal failure and their relationships with potential clinical risk factors, a multicentre follow-up study was performed, including patients enrolled in the previous cross-sectional survey.

Material and methods

Study protocol

A multicentre follow-up study was carried out which enrolled patients who had undergone BMD assessment (1st BMD) in a previous cross-sectional survey[6] on the prevalence of bone disease in HPN. All the centres participating in the previous survey were invited to contribute to the present study.

Patients were included in the follow-up study if all the following criteria were met:

(a) having been in the previous cross-sectional survey;
(b) having been routinely followed by the centre;
(c) having undergone a second BMD assessment (2nd BMD) at least 9 months after the 1st BMD assessment;
(d) having had both the BMD assessments performed by the same dual-energy X-ray absorptiometry (DEXA) instrument (Hologic QDR 1000 or 4500, Norland XR36, Lunar DPX) and at the same anatomical site (lumbar spine or femoral neck).

The participating centres were also asked to review the records of the patients included in the previous cross-sectional survey, in order to search for the results of the BMD assessment performed immediately before or after the beginning of HPN (within 1 month) by the same DEXA instrument used for the 1st BMD (baseline BMD).

Data collection

The patient records were reviewed using a structured questionnaire. The following data were collected with respect to the 1st and the 2nd BMD and to the follow-up period:

General factors and life-style factors: Age (years); sex; menopausal state; body weight (BW); BMI (kg/m^2); no. of significant variations of BW ($\pm$5 kg) during the follow-up; rehabilitation degree according to the Mughal and Irving classification[11] (grade 1–4 = best to poorest); no. of changes of the rehabilitation degree during the follow-up; cigarette smoking.

Underlying disease factors: Primary disease and its duration before starting HPN; age at starting HPN; cause of the intestinal failure; intestinal function (% of fat malabsorption); oral energy intake (dietary history); characteristics of the oral diet (free, low fat, low fibre, liquid, clear liquid, no oral food); systemic inflammation (ESR$\geqslant$20, serum CRP > normal or WBC $\geqslant$9000/mm^3: 0%, 25%, 50%, 75% or 100% of the duration of the follow-up); hospital stays: no. and duration (days); drugs: corticosteroids, immunosuppressive, oral calcium, calcitonin, anabolic steroids, bisphosphonates, oral or i.m. vitamin D, diuretics, SERMS, estrogens: dosage and duration of the treatment during the follow-up); presence of organ failure (liver, renal); and surgical procedures.

HPN factors: Total duration of HPN; characteristics of the HPN programme during the follow-up; no. of days of infusion/week; length of infusion (h/day of infusion); ratio between energy supplied weekly by HPN (kJ/day of infusion $\times$ no. of infusions per week) and weekly basal energy expenditure (BEE) evaluated by the Harris–Benedict formula (BEE $\times$ 7); amino acids, glucose, fats: g/kg BW/day

of infusion; Ca, P, Mg, Na and acetate: mmol/day of infusion; Ca/P ratio; vitamins and trace metals: no. of infusions/week; and no. of central venous catheter (CVC) major complications (catheter infections, thrombosis). Information about serum and parenteral solution aluminium concentrations were also asked.

Bone disease diagnosis and classification

The BMD *Z*-score (number of standard deviations from normal values corrected for sex and age) and the annualized percent BMD change were analysed. The *Z*-score was classified as:

- *normal*: a *Z*-score within 1 SD;
- *reduced*: a *Z*-score below −1 SD but less than −2 SD;
- *severely reduced*: a *Z*-score equal or below −2 SD.

At all centres, the BMD *Z*-score reference values were those provided by the manufacturer of the absorptiometer.

The annualized percent BMD change was the observed BMD change (g/cm^2) divided by the time of observation for each individual patient, equalized for 365 days. In each centre, the precision of the DEXA instrument was assessed by spine phantom BMD CV which was $<1\%$ in all the centres during the study period.

The occurrence of bone pain and bone fractures during the follow-up periods were noted.

Statistics

Data are reported as mean ± standard deviations and range (within parenthesis). Differences between means were analysed by the Mann–Whitney *U*-test. Differences between frequencies were analysed by the χ^2 test. Relationships were analysed using Pearson's simple regression and by backward multiple regression analyses. The SSPS/PC + statistical package (SSPS Inc. Chicago, USA) was used for the analyses. Two-tailed *P*-values <0.05 were accepted as significant.

Results

Patient population

Six out of the nine centres which contributed to the first cross-sectional survey participated in the present study. A total of 65 patients of Caucasian race met the criteria for inclusion, which represented 45% of the patient population included by these centres in the first survey. The reasons for patient exclusion from the analysis were: cessation of HPN during the follow-up, lack of patient informed consent, 2nd BMD assessment performed less than 9 months from the 1st BMD or performed by a DEXA instrument different from that used for the baseline BMD.

In all the patients, the indication for the 1st BMD assessment had been routine follow-up or participation in the cross-sectional study. DEXA- scans were performed with the following instruments: Hologic (QDR 1000 or 4500) in 29 patients (44.6%); Norland (XR36) in 22 (33.9%); and Lunar (DPX) in 14 (21. 5%). The characteristics of the patients at the 1st BMD are reported in Table 1.

The 2nd BMD was performed after a mean of 18.1 ± 5.5 (9–33) months from the 1st BMD. The site of the assessment was the LS in 50 patients and the FN in 44. Tables 2 and 3 report the characteristics of the patients, of the underlying disease and of the HPN programme during the follow-up, except for the serum and the parenteral solution aluminium concentrations which were obtained only in two and five patients, respectively.

Variations of the BMD Z-score and symptoms of bone disease during follow-up

Data are reported in Table 4. The BMD *Z*-score increased in more than one-half of the patients at both the LS and the FN. Simple regression between *Z*-scores and annualized percent BMD changes was $R = 0.867$ ($P < 0.001$) at LS and $R = 0.855$ ($P < 0.001$) at FN. The mean BMD *Z*-score significantly increased at the LS ($P = 0.040$) and remained unchanged at the FN ($P = 0.520$). In the group of patients who had BMD assessment at both sites, no significant relationship was observed between the *Z*-score variations ($R = 0.224$; $P = 0.217$).

During the follow-up, 40.0% of the patients complained of bone pain and three patients (postmenopausal women) had five non-traumatic bone fractures (spine, 2; rib, 1; forearm, 1). At the 1st BMD assessment, the *Z*-scores of patients with symptoms of bone disease during the follow-up were similar to the *Z*-scores of the asymptomatic patients. During the follow-up, the mean variations of the *Z*-scores were negative in the subgroup of symptomatic patients and positive in the group of asymptomatic patients, the difference being statistically significant only for the lumbar spine *Z*-score. In two out of the three patients who had bone fractures, the 1st BMD *Z*-scores were

Table 1 Characteristics of the patient population at the 1st BMD assessment.

No.	65
Age (years)	51.9 ± 15.3 (20–76)
Males/females (no.)	26/39
Post-menopausal females (no.)	25
Duration of HPN (months)	72.1 ± 61.9 (5–293)
Age at starting HPN (years)	46.3 ± 16.5 (4–74)
Primary disease (no. and %)	
Crohn's	13 (20.0%)
Mesenteric ischaemia	30 (46.2%)
Others[a]	22 (33.8%)
Age at diagnosis of the primary disease (years)	42.6 ± 17.8 (3–73)
Duration of the primary disease before HPN (months)	41.0 ± 58.1 (0–217)
Cause of intestinal failure (no. and %)	
Short bowel	58 (89.2%)
Motility disorder	5 (7.7%)
Extensive disease	1 (1.5%)
Fistulas	1 (1.5%)
BMI (kg/m^2)	20.9 ± 3.1 (9.8–28.4)
Rehabilitation degree (best to poorest: 1–4)	1.92 ± 0.97 (1–4)
BMD *Z*-Score at lumbar spine (in 52 pts.)	−1.48 ± 1.38 (−4.15 to +2.07)
> -1	21 (40.4%)
Between $\leqslant -1$ and < -2	10 (19.2%)
$\leqslant -2$	21 (40.4%)
BMD *Z*-Score at femoral neck (in 48 pts.)	−1.02 ± 1.38 (−3.99 to +2.70)
> -1	23 (47.9%)
Between $\leqslant -1$ and < -2	14 (29.2%)
$\leqslant -2$	11 (22.9%)

HPN = home parenteral nutrition.
Z-score = number of standard deviations from mean BMD normal values corrected for sex and age.
[a]Radiation enteritis, 6; pseudo-obstruction, 3; others, 13.

< -2.5 at both sites of assessment, whereas the third patient had only LS assessment which was −1.46.

Comparisons in patient subgroups

General factors, life style, primary disease and HPN-related factors as well as the BMD *Z*-score at baseline were compared between the two subgroups of patients who showed a decrease of the BMD *Z*-score and those who showed an increase or no change during follow-up.

At the FN, the two subgroups differed only with respect to the primary diseases (Tables 5–7). The mean annualized percent BMD change did not differ between pre-menopausal (0.98 ± 3.09) and post-menopausal (−0.25 ± 5.18) women ($P = 0.397$).

At the LS, the subgroup which showed a decrease and the subgroup which showed an increase or no change of the BMD *Z*-score significantly differed with respect to the *Z*-score value at the 1st BMD, age at the 1st BMD, sex, degree of rehabilitation at the 2nd BMD, age at starting HPN, primary disease,

Table 2 Characteristics of the patient population (65 pts.: 26 males and 39 females) at the 2nd BMD assessment and during the follow-up (between the 1st and the 2nd BMD).

Data at the 2nd BMD	
Duration of HPN (months)	89.5 ± 62.5 (21–314)
Age of the patients (years)	53.2 ± 15.4 (22–77)
Post-menopausal females (no.)	27
BMI (kg/m^2)	21.1 ± 2.59 (12.1–26.7)
Rehabilitation degree (best to poorest: 1–4)	1.72 ± 0.88 (1–4)
Duration of the follow-up	
9–11 months (no. of pts. and %)	6 (9.2%)
12–17 months (no. of pts. and %)	25 (38.5%)
18–23 months (no. of pts. and %)	22 (33.8%)
⩾23 months (no. of pts. and %)	12 (18.5%)
Data during the follow-up	
Variations of body weight ± 5 kg	
No. of patients	21
No. of variations/patient	2.95 ± 1.83 (1–6)
Variations of rehabilitation degree	
No. of patients	5
No. of variations/patient	1.0 ± 0.0
Cigarette smoking (no. of pts. and %)	9 (13.8%)
Patients receiving drugs (no. and %)	
Corticosteroids	5 (7.7%)
Immunosuppressive	1 (1.5%)
Diuretics	6 (9.2%)
Oestrogenic hormones	3 (4.6%)
Oral calcium	23 (35.4%)
Bisphosphonates	14 (21.5%)
Vitamin D, i.m.	19 (29.2%)
Vitamin D, oral	20 (30.8%)
Morbidity (no. of pts. and %)	
Chronic renal failure	7 (10.7%)
Surgical intervention[a]	4 (6.1%)
Deep vein thrombosis	2 (3.1%)
Central venous catheter infection	16 (24.6%)
Chronic systemic inflammation (% of the follow-up)	
0	34 (52.3%)
25%	8 (12.3%)
50%	8 (12.3%)
75%	9 (13.8%)
100%	6 (9.2%)
Hospitalization	
No. of pts. and %	29 (44.6%)
No. of days in hospitalized patients	23.8 ± 18.2 (2–67)

HPN = home parenteral nutrition.
[a]Cholecystectomy, 3; intestinal stricturoplasty, 1.

duration of the primary disease before starting HPN, the number of CVC infections per patient, number of patients having hospitalization and the number of hospitalization days per patient during the follow-up (Tables 8–10). The mean annualized percent BMD change was slightly positive in pre-menopausal (0.22 ± 4.96) and negative in post-menopausal (−3.05 ± 4.01) women ($P = 0.157$).

Regression analyses in the whole group

A significantly positive correlation was observed between the age at starting HPN and the LS BMD

Table 3 Characteristics of the HPN programme of the oral diet and of intestinal absorption during the follow-up (between the 1st BMD and the 2nd BMD).

Days of HPN infusion per week	5.54±1.47 (2–7)
Hours of HPN infusion per day	13.3±2.7 (9.0–24.0)
Nutrients in the HPN (per day of infusion)	
Volume (ml)	2146±916 (1000–7000)
Amino acids (g/kg body weight)	1.06±0.44 (0.0–2.06)
Glucose (g/kg body weight)	4.02±1.53 (1.36–8.77)
Lipids (g/kg body weight)	0.82±0.56 (0.0–2.37)
Na (mmol)	117±89 (11–450)
Ca (mmol)	7.86±2.74 (3.0–19.0)
Phosphate (mmol)	16.9±8.5 (0–40)
Ca/phosphate (mmol/mmol)	0.58±0.45 (0.10–3.40)
Mg (mmol)	9.74±3.40 (3.0–20)
Acetate (mmol)	109±59 (0–257)
Micronutrients (no. per week)[a]	
Vitamins	4.27±2.28 (0–7)
Trace metals	3.09±2.34 (0–7)
Total energy by HPN/BEE (per week)[b]	0.91±0.39 (0.10–1.85)
Oral energy intake (kJ/day)	6664±2323 (1674–11586)
Type of oral diet (no. of pts. and %)	
Free	27 (41.5%)
Low Fat	2 (3.1%)
Low fibre	3 (4.6%)
Liquid	30 (30.8%)
Clear liquid	11 (16.9%)
No oral food	2 (3.1%)
Fat malabsorption (no. of pts. and %)	
< 7%	11 (16.9%)
7–25%	10 (15.4%)
26–50%	31 (47.7%)
>50%	13 (20.0%)

BMD = bone mineral density.
[a]Commercial preparations for parenteral nutrition.
[b]kJ/day of infusion × no. of infusions per week/BEE × 7.

Z-score at the 1st BMD assessment: $R = 0.286$, $P = 0.044$.

A backward multiple regression analysis was performed using the variations of the LS BMD *Z*-score as a dependent variable and as independent variables those parameters, shown in Tables 5–7, which significantly differed between the subgroups of patients with decreased or increased/unchanged BMD *Z*-scores. Only the degree of rehabilitation ($P = 0.098$), sex ($P = 0.070$) and age at starting HPN ($P = 0.056$) entered in the system. After removing the rehabilitation degree, the relationships between LS BMD *Z*-score changes and sex ($P = 0.021$) and age at starting HPN ($P = 0.022$) were statistically significant and the equation of the multiple linear regression model was: LS BMD *Z*-score change = 0.9450–0.0088 × age at starting HPN—0.2772 × sex (male = 1; female = 2) (*F*-ratio = 7.11; $P = 0.001$), adjusted R^2 of the model was 0.203. The last backward multiple regression analysis was repeated replacing the annualized percent BMD changes for the *Z*-score changes as a dependent variable. The results confirmed sex ($P < 0.001$) and age at starting HPN ($P = 0.007$) as the only variables which entered in the system: annualized percent LS BMD change = 11.22–0.1080 × age at starting HPN—4.287 × sex (male = 1; female = 2) (*F*-ratio = 13.65; $P < 0.001$), adjusted R^2 0.340.

The relationship between age at starting HPN and age at time of entering in the study (1st BMD

Table 4 Variations of the BMD *Z*-scores and symptoms of bone disease during the follow-up (between the 1st BMD and the 2nd BMD.

BMD Z-score variations at lumbar spine (50 pts.)	
Absolute (2nd BMD–1st BMD)	$+0.15 \pm 0.43$ (-0.82 to $+1.30$)
Increase or no change (no. and %)[a]	32 (64.0%)
Decrease (no. and %)	18 (36.0%)
BMD Z-score variations at femoral neck (44 pts.)	
Absolute (2nd BMD–1st BMD)	$+0.05 \pm 0.47$ (-1.70 to $+0.98$)
Increase or no change (no. and %)[a]	24 (54.5%)
Decrease (no. and %)	20 (45.5%)
Bone pain during the follow-up (no. of patients and %)	26 (40.0%)
Fractures during the follow-up (no. of patients and %)	3 (4.6%)
BMD Z-scores in patients with bone pain or fracture (no. 27)	
Lumbar spine *Z*-score (17 pts.)	
Baseline	-1.54 ± 1.35 (-4.00 to $+0.99$)
Absolute variation (2nd BMD–1st BMD)	-0.03 ± 0.35 (-0.82 to $+0.76$)[b]
Increase (no. of pts. and %)	9 (52.9%)
Decrease (no. of pts. and %)	8 (47.1%)
Femoral neck *Z*-score (19 pts.)	
Baseline	-1.08 ± 1.72 (-3.60 to $+2.50$)
Absolute variation (2nd BMD–1st BMD)	-0.04 ± 0.50 (-1.70 to $+0.75$)
Increase (no. of pts. and %)	10 (52.6%)
Decrease (no. of pts. and %)	9 (47.4%)
BMD Z-scores in asymptomatic patients (no. 38)	
Lumbar spine *Z*-score (33 pts.)	
Baseline	-1.17 ± 1.37 (-3.42 to $+1.45$)
Absolute variation (2nd BMD–1st BMD)	$+0.24 \pm 0.44$ (-0.56 to $+1.30$)
Increase (no. of pts. and %)	23 (69.7%)
Decrease (no. of pts. and %)	10 (30.3%)
Femoral neck *Z*-score (25 pts.)	
Baseline	-0.83 ± 1.19 (-3.10 to $+2.48$)
Absolute variation (2nd BMD–1st BMD)	$+0.12 \pm 0.41$ (-0.60 to $+0.98$)
Increase (no. of pts. and %)	14 (56.0%)
Decrease (no. of pts. and %)	11 (44.0%)

Z-score = number of standard deviations from mean BMD normal values corrected for sex and age.
[a]No change: at lumbar spine, one patient; at femoral neck, two patients.
[b]$P = 0.039$ vs. asymptomatic patients.

assessment) was $R = 0.938$ ($P < 0.001$). Excluding age at starting HPN from the above multiple regressions, the results were: LS BMD *Z*-score change = 0.9402–0.0078 × age at the 1st BMD—0.2633 × sex (male = 1; female = 2) ($P = 0.056$ for age at 1st BMD, $P = 0.026$ for sex; *F*-ratio = 6.07, $P = 0.004$, adjusted $R^2 = 0.171$, for the model); annualized percent LS BMD change = 11.60–0.0953 × age at the 1st BMD—4.286 × sex (male = 1; female = 2) ($P = 0.027$ for age at 1st BMD, $P < 0.001$ for sex; *F*-ratio = 11.80, $P < 0.001$, adjusted $R^2 = 0.306$ for the model).

Lumbar spine BMD changes between baseline BMD and the 1st BMD

Baseline BMD was available for eight patients who had the LS BMD assessed within 1 month from starting HPN: males five and females three; age at starting HPN, 45.8 ± 14.7 years (24–63); mesenteric ischaemia 4, radiation enteritis 1, volvolus 1, others 2; short bowel 8. The LS BMD *Z*-score was > -1 in three patients, between -1 and -2 in four patients and < -2 in one patient. The relationship between the age at starting HPN and the baseline *Z*-score was positive: $R = 0.305$; $P = 0.463$. The

Table 5 1st BMD Z-score, annualized percent BMD change, type of DEXA instrument, duration of the follow-up (between the 1st BMD and the 2nd BMD) and general, life style and primary disease characteristics in the patient subgroups on the basis of the FN BMD Z-score variation.

	Femoral neck BMD Z-score variation		
	Decreased (20 pts.)	Increased/unchanged (24 pts.)	*P*
DEXA instrument (no. and % of pts.)			0.599
Hologic	4 (20.0%)	5 (20.8%)	
Norland	8 (40.0%)	12 (50.0%)	
Lunar	8 (40.0%)	7 (29.2%)	
Annualized BMD changes (%/year)	-3.58 ± 4.67	4.13 ± 1.52	< 0.001
1st BMD Z-score	-0.63 ± 1.41	-1.28 ± 1.52	0.140
Duration of follow-up (months)	17.5 ± 6.2	17.0 ± 5.2	0.758
Age at the 1st BMD (years)	55.5 ± 16.7	54.4 ± 17.1	0.924
Females (no. and % of pts.)	12 (60.0%)	16 (66.7%)	0.647
Post-menopausal (no. and % of females)	8 (66.7%)	12 (75.0%)	0.629
BMI (kg/m^2)	21.4 ± 1.8	21.1 ± 1.9	0.089
Variation of BMI (kg/m^2)	0.05 ± 1.87	0.81 ± 1.97	0.187
No. of significant variations of body weight (± 5 kg)	1.40 ± 2.03	1.20 ± 1.93	0.671
Rehabilitation degree at the 2nd BMD (best to poorest: 1–4)	1.75 ± 0.85	1.66 ± 0.86	0.660
No. of variations of rehabilitation degree	0.10 ± 0.30	0.04 ± 0.20	0.449
Duration of HPN (months)	75.4 ± 48.7	108.7 ± 80.1	0.171
Age at starting HPN (years)	48.8 ± 18.0	45.5 ± 18.7	0.450
Primary disease (no. and %)			0.022
Crohn's	4 (20.0%)	7 (20.2%)	
Mesenteric ischaemia	13 (65.0%)	6 (25.5%)	
Others	3 (15.0%)	11 (45.8%)	
Duration of primary disease before starting HPN (months)	37.4 ± 53.0	61.5 ± 70.2	0.115
Short bowel (no. and % of pts.)	19 (95.0%)	198 (79.2%)	0.127
Cigarette smoking (no. and % of pts.)	3 (15.0%)	5 (20.8%)	0.617

Z-score = number of standard deviations from mean BMD normal values corrected for sex and age.
DEXA = dual-energy-X-ray absorptiometry.

mean variation of the Z-score was—0.15 ± 1.01 between the baseline BMD and the 1st BMD. The relationship between the age at starting HPN and the Z-score variations was negative: $R = -0.256$; $P = 0.540$.

Discussion

The results of this short-term follow-up study in an adult patient population receiving HPN for chronic benign intestinal failure showed an increase of the

Table 6 Drugs and morbidity during follow-up (between the 1st BMD and the 2nd BMD) in the patient subgroups on the basis of the FN BMD *Z*-score variations.

	Femoral neck BMD *Z*-score variation		
	Decreased (20 pts.)	Increased/unchanged (24 pts.)	*P*
Patients receiving drugs (no. and %)[a]			
Corticosteroids	2 (10.0%)	3 (12.5%)	0.794
Immunosuppressive	1 (5.0%)	0	0.926
Diuretics	3 (15.0%)	3 (12.5%)	0.809
Oestrogenic hormones	1 (5.0%)	1 (4.2%)	0.894
Oral calcium	6 (30.0%)	6 (25.0%)	0.710
Bisphosphonate	2 (10.0%)	6 (25.0%)	0.198
Vitamin D, i.m.	4 (20.0%)	6 (25.0%)	0.693
Vitamin D, oral	8 (40.0%)	6 (25.0%)	0.287
Chronic renal failure (no. of pts. and %)	2 (10.0%)	4 (16.7%)	0.521
Surgical intervention (no. of pts. and %)	1 (5.0%)	2 (8.3%)	0.662
Deep vein thrombosis (no. and %)	0	0	1.00
CVC infection (no./patient)	0.45 ± 0.88	0.16 ± 0.38	0.383
Chronic systemic inflammation (% of follow-up/patient)	27.5 ± 39.6	33.3 ± 34.3	0.514
Hospitalization			
No. and % of patients	7 (35.0%)	12 (50.0%)	0.317
No. of days (in hospitalized patients)	23.2 ± 13.6	25.5 ± 21.1	0.832

Z-score = number of standard deviations from mean BMD normal values corrected for sex and age.
CVC = central venous catheter.
[a]Patients receiving drugs for at least 33% of the duration of the follow-up.

BMD *Z*-score in more than one-half of the patients and indicated that age and sex were the only clinical risk factors independently correlated with the changes in the LS BMD *Z*-score, which were negative in older patients and females. Moreover, the positive correlation between the age at starting HPN and the LS BMD *Z*-score, observed in the previous study[6] and confirmed in the present one, suggests that patients who developed intestinal failure at a younger age had a lower spine BMD at starting HPN, but they also showed a greater probability of increasing axial bone calcium content during the treatment than patients who started HPN at an older age. The study protocol was based on the analysis of the *Z*-score, which allows the comparison of the patient BMD to normal BMD values corrected for sex and age. Because of the multicentre design of the study, different DEXA instruments were used and the *Z*-score evaluation relied on different data bases. In order to verify if this had interfered with the results, the annualized percent BMD changes were also analysed. The results confirmed and strengthened those obtained by the BMD *Z*-score even though the use of a phantom to calibrate all the instruments together would have been the most appropriate methods to avoid bias due to the use of different instruments.

In spite of many potential HPN-related mechanisms for the development of a metabolic bone disease, the BMD significantly increased at the axial bone and remained stable at the appendicular bone. Also the results of the previously published longitudinal studies performed by single centre and including small patient groups showed that long-term HPN do not necessarily cause a worsening of bone health and in some cases may be beneficial.[7–10] Foldes et al.[7] studied 10 patients. After a follow-up period of 5–19 months cancellous and cortical BMD significantly decreased in eight and in seven patients, respectively, and increased or remained stable in the others. The initial BMD was lower in patients in whom HPN was started several years after the diagnosis of intestinal disease, but the rate of change of BMD values did not differ between

Table 7 Characteristics of the HPN programme, oral diet and intestinal function during follow-up (between the 1st BMD and the 2nd BMD) in the patient subgroups on the basis of FN BMD *Z*-score variations.

	Femoral neck BMD *Z*-score variation		
	Decreased (20 pts.)	Increased/unchanged (24 pts.)	*P*
Days of HPN infusion per week	5.50±1.57	5.33±1.5	0.830
Hours of HPN infusion per day	13.4±2.5	13.8±3.0	0.854
Nutrients in the HPN (per day of infusion)			
Volume (ml)	2137±758	2108±708	0.934
Amino acids (g/kg body weight)	0.97±0.40	0.96±0.35	0.804
Glucose (g/kg body weight)	3.74±1.37	4.08±1.38	0.486
Lipids (g/kg body weight)	0.86±0.58	0.72±0.55	0.670
Na (mmol)	103±81	106±63	0.743
Ca (mmol)	7.65±2.41	7.33±1.99	0.836
Phosphate (mmol)	15.1±9.2	16.6±6.9	0.585
Ca/Phosphate (mmol/mmol)	0.56±0.25	0.56±0.32	0.715
Mg (mmol)	9.85±3.18	8.91±2.39	0.451
Acetate (mmol)	93.64±71.9	101.8±56.3	0.504
Micronutrients (no. per week)[a]			
Vitamins	4.22±2.23	3.95±2.40	0.773
Trace metals	3.40±2.52	2.97±2.65	0.591
Total energy by HPN/BEE (per week)[b]	0.85±0.38	0.86±0.37	0.887
Oral energy intake (Calories/day)	1621±615	1552±566	0.563
Type of oral diet (no. of pts. and %)			0.601
Free	12 (60.0%)	11 (45.8%)	
Low fat	0	1 (4.2%)	
Low fibre	2 (10.0%)	1 (4.2%)	
Liquid	4 (20.0%)	6 (25.0%)	
Clear liquid	2 (10.0%)	3 (12.5%)	
No oral food	0	2 (8.3%)	
Fat malabsorption (no. of pts. and %)			0.783
<7%	3 (15.0%)	4 (16.7%)	
7–25%	2 (10.0%)	5 (20.8%)	
26–50%	10 (50.0%)	10 (41.7%)	
>50%	5 (25.0%)	5 (20.8%)	

[a]Commercial preparations for parenteral nutrition.
[b]Calories per day of infusion × no. of infusions per week/BEE × 7).

patients with and without prolonged intestinal disease before starting HPN. Over a period of 6–28 months, Shike et al.[8] found a significant decrease in bone mass in five patients whose bone mass was initially in the normal range and a not significantly increase in nine patients with initial values below normal. Saitta et al.[9] studied 14 patients over a period of 7–61 months. On entry into the study, the BMD measures at both cancellous and cortical bone were negatively correlated with the duration of HPN. At the follow-up assessment, BMD remained stable in nine, increased in two and decreased in three patients. In the whole group, the changes of BMD at the cortical bone negatively correlated with the duration of the follow-up. No correlation was observed with the changes at the cancellous bone. Staun et al.[10] studied 15 patients with inflammatory bowel disease (13 Crohn's disease) receiving HPN for short bowel syndrome, over a period of 20–106 months. On entry into the study, both mean LS and FN BMD *Z*-score were significantly reduced, but *Z*-score values did not correlate with the duration of the HPN. During the follow-up, LS and femoral neck BMD *Z*-score decreased in eight and nine patients, respectively, and increased or was unchanged in the other patients. At both sites, the

Table 8 1st BMD *Z*-score, annualized percent BMD change, type of DEXA instrument, duration of the follow-up (between the 1st BMD and the 2nd BMD), and general, life style and primary disease characteristics in the patient subgroups on the basis of the LS BMD *Z*-score variation.

	Lumbar spine BMD *Z*-score variation		
	Decreased (18 pts.)	Increased/unchanged (32 pts.)	*P*
DEXA instrument (no. and % of pts.)			0.834
Hologic	5 (27.8%)	8 (25.0%)	
Norland	8 (44.4%)	15 (46.9%)	
Lunar	5 (27.8%)	9 (28.1%)	
Annualized BMD changes (%/year)	-4.54 ± 2.91	3.07 ± 3.47	< 0.001
1st BMD *Z*-score	-0.71 ± 1.43	-1.85 ± 1.21	0.005
Duration of follow-up (months)	17.9 ± 5.9	17.8 ± 5.9	0.895
Age at the 1st BMD (years)	55.4 ± 12.0	45.4 ± 14.6	0.018
Females (no. and % of pts.)	15 (83.3%)	12 (37.5%)	0.005
Post-menopausal (no. and % of females)	9 (60.0%)	7 (58.3%)	1.00
BMI (kg/m^2)	21.2 ± 2.7	20.4 ± 2.5	0.312
Variation of BMI (kg/m^2)	-0.58 ± 1.93	0.28 ± 1.33	0.159
No. of significant variations of body weight (± 5 kg)	1.22 ± 1.96	1.09 ± 1.87	0.768
Rehabilitation degree at the 2nd BMD (best to poorest: 1–4)	1.94 ± 0.94	1.34 ± 0.54	0.015
No. of variations of rehabilitation degree	0.11 ± 0.32	0.06 ± 0.25	0.547
Duration of HPN (months)	91.7 ± 72.9	97.5 ± 63.2	0.538
Age at starting HPN (years)	48.6 ± 13.9	37.8 ± 14.7	0.010
Primary disease (no. and %)			0.044
Crohn's	2 (11.1%)	11 (34.4%)	
Mesenteric ischaemia	12 (66.7%)	10 (31.3%)	
Others	4 (22.2%)	11 (34.4%)	
Duration of primary disease before starting HPN (months)	16.5 ± 28.1	59.7 ± 68.6	0.008
Short bowel (no. and % of pts.)	17 (94.4%)	28 (87.5%)	0.768
Cigarette smoking (no. and % of pts.)	3 (16.6%)	4 (12.5%)	1.00

Z-score = number of standard deviations from mean BMD normal values corrected for sex and age.
DEXA = dual-energy X-ray absorptiometry.

Z-score changes did not correlate with the duration of the HPN. Our data obtained by means of densitometry differs from those obtained from bone histology. The present follow-up and our previous cross-sectional investigation[6] were performed on patients who underwent either routine BMD assessment or BMD assessment for participation in the studies. On the contrary, almost all the

Table 9 Drugs and morbidity during follow-up (between the 1st BMD and the 2nd BMD) in the patient subgroups on the basis of the LS BMD *Z*-score variations.

	Lumbar spine BMD *Z*-score variation		
	Decrease (18 pts.)	Increase/unchanged (32 pts.)	*P*
Patients receiving drugs (no. and %)[a]			
Corticosteroids	1 (5.6%)	4 (12.5%)	0.768
Immunosuppressive	0	1 (3.1%)	1.00
Diuretics	1 (5.6%)	0	0.768
Oestrogenic hormones	3 (16.7%)	0	0.078
Oral calcium	4 (22.2%)	11 (34.4%)	0.563
Bisphosphonate	4 (22.2%)	6 (18.8%)	1.00
Vitamin D, i.m.	4 (22.2%)	4 (12.5%)	0.618
Vitamin D, oral	3 (16.7%)	6 (18.8%)	1.00
Chronic renal failure (no. of pts. and %)	2 (11.1%)	3 (9.4%)	1.00
Surgical intervention (no. of pts. and %)	1 (5.6%)	2 (6.3%)	1.00
Deep vein thrombosis (no. and %)	2 (11.1%)	0	0.241
CVC infection (no./patient)	0.89 ± 1.13	0.16 ± 0.45	0.002
Chronic systemic inflammation (% of follow-up/patient)	20.9 ± 33.5	26.6 ± 33.6	0.514
Hospitalization			
No. and % of patients	13 (72.2%)	9 (28.1%)	0.007
No. of days (in hospitalized patients)	23.8 ± 16.0	17.0 ± 14.9	0.216

Z-score = number of standard deviations from mean BMD normal values corrected for sex and age.
CVC = central venous catheter.
[a]Patients receiving drugs for at least 33% of the duration of the follow-up.

studies[12–15] on bone histology in patients on HPN without evidence of excessive aluminium exposure were performed on patients having symptoms and/or biochemical signs of bone disease. These investigations showed the presence of either osteomalacia or osteoporosis associated with a low bone formation rate and hypercalciuria in most of the patients. A direct pathogenetic role of HPN was hypothesized through toxicity from daily intravenous infusion of vitamin D,[12] hypercalciuria induced by the intravenous infusion of nutrients,[13] the development of an impaired PTH secretion or a decreased response to the hormone.[14] Other hypotheses were excess (strontium, fluoride, cadmium) or deficiency (zinc, copper, manganese) of micronutrients,[13,15] which are considered to play a role in bone metabolism or a direct role of HPN in inducing the release and/or regulating the activity of cytokines known to impair bone metabolism.[16] The comparison of the results obtained from histology with those obtained by means of densitometry suggests that, while a single patient may develop an HPN-related impairment of bone metabolism, the risk of an HPN-related decrease of BMD is not evident in the patient population. Alternative explanations may be the lack of bone densitometry in detecting qualitative bone changes.[17] Nevertheless, our findings indicate that, in patients on HPN, bone symptoms predict a decrease of BMD and that BMD values may predict the risk of bone fractures, in agreement with the World Health Organization diagnostic categories of bone disease, based on the measurement of the BMD, which were established for post-menopausal women in whom osteoporosis is by far the most common bone disease.[18]

The results of the multiple regression analysis showed that general factors, but not underlying disease or HPN-related factors, were independently associated with the variations of the LS BMD during HPN. As in the general population,[18,19] female sex and ageing were the main clinical risk factors for a decrease in the BMD at the LS (trabecular bone). The two major determinants of

Table 10 Characteristics of the HPN programme, oral diet and intestinal function during follow-up (between the 1st BMD and the 2nd BMD) in the patient subgroups on the basis of LS BMD *Z*-score variations.

	Lumbar spine BMD *Z*-score variation		
	Decrease (18 pts.)	Increase/unchanged (32 pts.)	*P*
Days of HPN infusion per week	6.06 ± 1.47	5.38 ± 1.41	0.060
Hours of HPN infusion per day	13.9 ± 3.6	13.0 ± 2.4	0.641
Nutrients in the HPN (per day of infusion)			
Volume (ml)	2401 ± 1331	2132 ± 740	0.701
Amino acids (g/kg body weight)	0.96 ± 0.46	1.05 ± 0.35	0.486
Glucose (g/kg body weight)	3.91 ± 1.78	4.42 ± 1.42	0.104
Lipids (g/kg body weight)	0.83 ± 0.69	0.81 ± 0.55	0.960
Na (mmol)	125 ± 95	120 ± 99	0.494
Ca (mmol)	7.22 ± 1.99	8.13 ± 2.45	0.320
Phosphate (mmol)	17.3 ± 8.7	17.0 ± 9.1	0.935
Ca/phosphate (mmol/mmol)	0.49 ± 0.26	0.54 ± 0.22	0.411
Mg (mmol)	9.44 ± 2.68	10.03 ± 3.61	0.919
Acetate (mmol)	95.12 ± 55.3	104.7 ± 62.5	0.643
Micronutrients (no. per week)[a]			
Vitamins	3.69 ± 2.70	4.28 ± 2.25	0.505
Trace metals	3.06 ± 2.60	3.56 ± 2.44	0.526
Total energy by HPN/BEE (per week)[b]	0.96 ± 0.45	0.89 ± 0.35	0.585
Oral energy intake (calories/day)	1511 ± 633	1698 ± 556	0.157
Type of oral diet (no. of pts. and %)			0.799
Free	10 (55.6%)	17 (53.1%)	
Low fat	1 (5.6%)	1 (3.1%)	
Low fibre	0	2 (6.3%)	
Liquid	3 (16.7%)	8 (25.0%)	
Clear liquid	3 (16.7%)	3 (9.4%)	
No oral food	1 (5.6%)	1 (3.1%)	
Fat malabsorption (no. of pts. and %)			0.142
< 7%	1 (5.6%)	4 (12.5%)	
7–25%	2 (11.1%)	6 (18.8%)	
26–50%	10 (55.6%)	18 (56.3%)	
>50%	5 (27.8%)	4 (12.5%)	

[a]Commercial preparations for parenteral nutrition.
[b]Calories per day of infusion × No. of infusions per week/BEE × 7.

risk in the development of osteoporosis are peak bone mass and rate of bone loss.[18,19] Thus, women are more likely to have osteoporosis than men because of a lower peak bone mass and a greater rate of bone loss, especially after menopause. The rate of bone loss also rises in men in old age. These two determinants are influenced by a number of genetic and environmental factors, although genetic factors play the major role including that indictating how an individual will respond to various exogenous stressors.[18,19] This may explain why sex and age at starting HPN were the only clinical factors independently related to the variations of the LS BMD *Z*-score and why, in our model, these two factors justified only 20% of the variations of the *Z*-score (34% of the annualized percent BMD change), indicating that other factors contributing to bone loss were not detected by or included in our investigation. Schulte et al.[20] showed that the extent of bone loss in patients with inflammatory bowel disease was associated with genetic variations of interleukin (IL)-1 receptor antagonist and IL-6 genes, but neither the clinical parameters nor biochemical markers of

bone metabolism predicted the rate of bone loss. They suggested that the genetic equipment of the bone determines the bone vulnerability to different systemic stress factors, thus determining patient risk for bone loss. Similar mechanisms may be hypothesized in HPN patients. Animal studies have shown that parenteral nutrition enhances the catabolic effects of tumour necrosis factor (TNF)α.[21] Increased serum and urine concentrations of IL-6 and soluble TNF receptor II, not associated with clinical and biochemical signs of inflammation, were observed in patients on long-term HPN.[22] Increased mRNA expression for inflammatory cytokines (IL-1, IL-6, TNF-α) in the intestine of parenterally fed rats have been demonstrated.[23] These findings would suggest that patients may differ in the way in which they react to HPN-related factors interfering with bone metabolism as well as to measures for preventing and treating bone disease. Indeed, our patients subgroups with increased or decreased BMD *Z*-scores did not differ with respect to the drugs received during the follow-up and a randomized controlled study on the effect of bisphosphonate clodronate on BMD and markers of bone turnover of patients on HPN gave some results which differed from what would have been expected.[24] No correlation was found between the bone turnover rate and the increase in BMD, a finding which is in contrast with that observed in post-menopausal osteoporosis, in which patients with a high rate of bone turnover respond to the treatment better.[25] Clodronate caused a decrease of the markers of bone resorption but also an unexplained increase of osteocalcin, the marker of bone formation.

Taken together, the results of the previous cross-sectional study[6] and of the present follow-up suggest that patients who developed intestinal failure at a younger age had a lower spine BMD when starting HPN, but they also showed a greater probability of increasing the axial calcium content during the treatment. Causes of intestinal failure occurring early in life may be associated with a reduced BMD through mechanisms directly increasing bone resorption, as in Crohn's disease, or indirectly decreasing bone formation, as in malnutrition due to reduced dietary intake or malabsorption.[26] The improvement of the nutritional status associated with HPN may allow the recovery of axial BMD in younger patients.[27] On the other hand, the main cause of intestinal failure in older patients is mesenteric ischaemia which, in the majority of cases, is a sudden event occurring in well-nourished subjects who may have no factor interfering with bone metabolism other than ageing. In the individual patient, the BMD variations were not consistent between the LS and the FN. The known differences between trabecular and cortical bone remodelling[19] may explain these data and why LS and FN BMD changes were not associated with the same risk factors. It should also be considered that bone turnover was not investigated in the present study. Considering the previous findings suggesting a potential pathogenetic role of intravenous vitamin D[12] and the development of impaired PTH secretion or function[14] in patients on long-term HPN, the involvement of these mechanisms cannot be excluded by the present investigation. Follow-up studies with measurements of biochemical markers of bone turnover in patients on long-term HPN are required.

In conclusion, this study did not show a significant decrease of the BMD *Z*-score in an adult patient population on long-term HPN and indicated that BMD variations were related to general clinical risk factors, such as age and sex, rather than to HPN-related factors. Studies investigating both the biochemical markers of bone turnover and the genetic risk factors for bone loss in patients receiving HPN could clarify the impact of HPN on bone metabolism.

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