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Original article

Osteoporosis in patients with intestinal insufficiency and intestinal failure: Prevalence and clinical risk factors

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SUMMARY

Background & aims: Intestinal insufficiency and intestinal failure are associated with malabsorption of micro- and macronutrients that may negatively influence bone metabolism and increase the risk for developing osteoporosis. However, information regarding prevalence and contribution of individual risk factors is scarce. We investigated the prevalence of osteoporosis in patients with intestinal insufficiency and intestinal failure and identified associated risk factors.

Methods: This was a retrospective cross-sectional study including 167 clinically stable outpatients with intestinal insufficiency or intestinal failure. Bone mineral density (BMD) was measured by dual X-ray absorptiometry and the prevalence of osteoporosis was compared to a gender and age matched population. Several clinical and demographic parameters, including body mass index (BMI), vitamin-D, smoking habits and medications, were analyzed for association with BMD.

Results: The prevalence of osteoporosis was 56.9% in the combined patient group compared to 24.1% in the control group (OR 4.2 [95% CI, 2.3 to 7.7]; $p < 0.001$). BMD in the hip was independently associated with BMI (0.13 [95% CI, 0.09 to 0.18]; $p < 0.001$) and vitamin-D levels (−0.41 [95% CI, −0.76 to −0.06]; $p = 0.03$). Similar associations were seen for BMD in the spine (0.15 [95% CI, 0.08 − 0.22]; $p < 0.001$) and (−0.60 [95% CI, −0.76 to −0.06]; $p = 0.02$), respectively. Trends for low BMD were observed in smokers, and in patients using glucocorticoids, opioids, and proton pump inhibitors.

Conclusions: Patients with intestinal insufficiency and intestinal failure are at immense risk of developing osteoporosis. Low BMI and vitamin-D deficiency were identified as independent risk factors.

Intestinal insufficiency and intestinal failure are characterized by physical and/or functional loss of a significant portion of the intestine [1–3]. Albeit the conditions are a continuum of the same pathophysiological process, they are abruptly distinguished by one specific event; the necessity of intravenous nutritional supplementation. Hence, patients with impaired intestinal absorption who can maintain health and growth by enteral nutritional strategies, e.g. oral nutritional supplements, are defined as having intestinal insufficiency, whereas conditions requiring intravenous supplementation, e.g. home parenteral nutrition, are defined as intestinal failure [1]. Both conditions are characterized by a deprived capability of nutrient processing and incapability of micro- and macronutrient absorption [2,3].

Malabsorption of micro- and macronutrients may negatively influence bone metabolism and in combination with other clinical risk factors (e.g. consumption of various medications, smoking, and/or consumption of alcohol) increase the risk of developing osteoporosis [4]. Accordingly, bone loss is a common complication of various intestinal diseases [5] and a high prevalence of osteoporosis has been reported in patients with intestinal failure [5–8]. However, previous studies failed to include a population derived control group and the specific risk factors associated with bone loss have only been scarcely investigated in this context.

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In a well characterized cohort of patients with intestinal insufficiency or intestinal failure the present study was designed to: 1) investigate the prevalence of osteoporosis and compare this to an age- and gender matched population derived cohort of Danish citizens [9], 2) compare the prevalence of osteoporosis in patients with intestinal insufficiency and intestinal failure, and 3) characterize demographic and clinical risk factors associated with a low bone mass.

1. Materials and methods

1.1. Setting

This was a retrospective cross-sectional study of consecutively recruited, clinically stable outpatients with intestinal insufficiency or intestinal failure on oral nutritional supplements or home parenteral nutrition, respectively. The study was performed at the Center for Nutrition and Bowel Disease (CET), Aalborg University Hospital, Denmark and was approved by the Data-Registry of the Northern Denmark Region (Journal no.: 2016-49).

1.2. Demographic and clinical parameters

Patient demographics and clinical parameters were obtained through interviews at the outpatient clinic and by reviewing individual patient records. This included smoking habits (smoking within four weeks of examination), excessive alcohol consumption (male >14 units and female >7 units per week), presence of comorbidities including chronic obstructive pulmonary disease (COPD) and diabetes, and former/current pharmacological treatment with glucocorticoids, opioids, or proton pump inhibitors (PPI).

1.3. Anthropometric assessment

Body weight was measured to nearest 0.1 kg using a digital electronic weight (Seca 701, CE0108, Seca, Birmingham, United Kingdom). Height was measured to nearest 0.1 cm using a wall-mounted stadiometer (Seca 222, CE0123, Seca, Birmingham, United Kingdom). The patients were measured wearing lightweight indoor clothing and without shoes. Body mass index (BMI) was calculated using measured body weight in kilograms divided by height in meters squared (kg/m^2).

1.4. Vitamin-D assessment

Venous blood samples were collected from the patients in Li-heparin tubes and plasma samples free of hemolysis were analyzed for 25-hydroxy-vitamin-D (D2 + D3). The samples were analyzed at Clinical Biochemical Department, Aalborg University Hospital using electrochemiluminescence-binding assay ECLIA (Roche Diagnostics – Vitamin-D total, Cobas 8000 e 602).

Classification of vitamin-D deficiency was performed as proposed by Lips et al. [10]: vitamin-D levels <25 nmol/l was defined as moderate/severe vitamin-D deficiency, 25–50 nmol/l as mild vitamin-D deficiency and >50 nmol/l as reference.

1.5. Dual-energy X-ray absorptiometry

BMD (g/cm^2) in lumbar spine (L1–L4) and total hip was assessed by dual-energy X-ray absorptiometry using a Hologic Discovery DXA-scanner (Hologic Inc., Marlborough, MA, USA) and expressed as age- and sex-adjusted Z-scores based on the manufacturers reference material. Osteoporosis was defined as T-score 2.5 standard deviations (SD) or more below the young adult mean (T-score ≤ -2.5) and osteopenia was defined as a T-score between −1.0 and −2.5 standard deviations according to the World Health Organization [11]. A daily quality control program was in place and coefficient of variation for the scans was <1%.

1.6. Statistical analysis

Results are presented as means ± standard deviation unless stated otherwise. Assumption of normality was checked through inspection of QQ-plots. Differences between demographical-, clinical-, anthropometrical-, and DXA data were compared by Student's t-tests, Fisher's exact test or chi-squared test as appropriate. The prevalence of osteoporosis was compared to a control population of healthy citizens including the entire Danish population [9]. The study, from which the control group was derived, offered prevalence estimates of osteoporosis divided into five-year intervals subcategorized by gender. By comparing the prevalence of osteoporosis in our study to the prevalence found in the control amongst 60 yr old Danish citizens, an age-adjusted control was achieved. Next, by mathematically adjusting for the difference in distribution of gender between the control population and our study, we achieved an age- and gender matched control population comprising the entire Danish population. Prevalence estimates were reported as population proportions and Odds Ratios (OR) with 95% confidence intervals (CI). Associations between BMD and putative risk factors for a decreased BMD were analyzed using uni- and multivariate linear regression analysis. Risk factors associated with BMD in univariate analysis were included in multivariate analysis and bootstrapping based on 5000 samples was used for internal validation of the multivariate estimates. To aid in interpretation of the retrieved findings, ordinal logistic regression was used to generate probability plots illustrating the probability of having osteopenia or osteoporosis as a function of BMI. All reported p-values were two-sided and a p-value <0.05 was considered as an indication of statistical significance. The software package STATA version 14.0 (StataCorp LP, College Station, TX) was used for the statistical analysis.

2. Results

2.1. Patient characteristics

A total of 167 patients were included (105 females and 62 males) and the mean age was 59.9 ± 15.1 yrs (60.3 ± 15.0 yrs for women, 59.2 ± 15.4 yrs for men). Table 1 reports demographics, clinical characteristics, anthropometrics, comorbidities, pharmacological treatment, vitamin-D levels, and DXA results for all patients. The etiologies of intestinal insufficiency and intestinal failure were comparable *viz* (IBD: [22.5% vs. 19.8%], cancer [28.2% vs. 16.7%], and ischemic bowel disease [12.7% vs. 15.6%]; $p = 0.27$) (Table 2). In contrast, the pathophysiological classification of bowel constitution differed significantly between patients with intestinal insufficiency and intestinal failure ($p = 0.007$) (Table 3).

2.2. Prevalence of osteopenia and osteoporosis

In the combined patient cohort, the prevalence of osteoporosis was 56.9% compared to 24.1% in the control group (OR 4.2 [95% CI, 2.3 to 7.7]; $p < 0.001$) (Fig. 1). The prevalence of osteopenia was 31.7% in the combined patient cohort; no estimates were available for osteopenia in the control group. The prevalence of osteoporosis was 61.5% in patients with intestinal failure compared to 50.7% in patients with intestinal insufficiency (OR 1.5 [95% CI, 0.86 to 2.63]; $p = 0.15$). The prevalence of osteopenia was 30.2% in patients with intestinal failure compared to 33.8% in patients with intestinal insufficiency (OR 0.8 [95% CI, 0.46 to 1.05]; $p = 0.54$).

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