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Original Research Article

Prevalence and risk factors of bone disease in patients with chronic pancreatitis: a cross sectional study

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ABSTRACT

Background: Osteopenia and osteoporosis is a highly prevalent condition and presents a tremendous public health burden. The association of bone disease has been recognized in several diseases of the git, resulting in established guidelines for screening in patients with malabsorptive disorders such as inflammatory bowel disease (IBD) and celiac disease. Increasingly, the risk of bone disease has been recognized in patients with chronic pancreatitis, who share similar risk factors as patients with other gastrointestinal disorders.
Methods: This single-centre study was carried out in Kilpauk medical college. This study population consisted of 47 patients who were image confirmed cases of chronic pancreatitis. History of smoking, alcohol use was taken, body mass index, fecal elastase was measured. Dual-energy X-ray absorptiometry scan was used to examine bone mineral density (BMD) for the lumbar spine and bilateral femoral neck.
Results: Of the 47 patients, 19 patients were chronic smokers and 28 patients had history of significant alcohol use. The prevalence of osteoporosis in patient group was 29.8% in patients with CP compared to Indian prevalence of 18.3% in previous studies. The prevalence of osteopenia was 48.9% in patients with CP compared to Indian prevalence of 49.9% in previous studies.
Conclusions: Bone disease in CP can be attributed to several risk factors which act synergistically in propagating abnormal bone metabolism. Osteoporosis and osteopenia are underappreciated sources of morbidity in patients with chronic pancreatitis. Bone health management guidelines are urgently required in patients with chronic pancreatitis.

Keywords: Chronic pancreatitis, DEXA scan, Osteoporosis

INTRODUCTION

Osteoporosis is a systemic disease of skeletal system. It is characterized by progressive micro-architectural deterioration of bone tissues. It results in low bone mass consequently increasing the bone fragility. These patients are known to be more susceptible for fractures.[1] Dual energy X-ray absorptiometry (DEXA) evaluates bone mass. It is the gold standard for BMD assessment.[2] WHO has categorized bone loss based on BMD as osteoporosis when BMD T-score of <-2.5 standard deviation (SD) and as osteopenia when BMD T-score of -1.0 to -2.5 SD below the average value.[3]

Many patients with chronic pancreatitis have shown to be having a higher prevalence of osteoporosis compared to general population thus increasing the risk of bone fracture.[2] The pathophysiology of bone disease in chronic pancreatitis is multifactorial. Various risk factors for secondary osteoporosis include increasing age, low body mass index from sitophobia, maldigestion due to exocrine pancreatic insufficiency with resulting low vitamin D, smoking as well as alcohol abuse.[2]

Presently there are guidelines for prevention of bone disease in patients with celiac disease (CD), IBD, and post-gastrectomy states.[2] Increasingly, the risk of bone

disease has been recognized in patients with chronic pancreatitis, who share similar risk factors as patients with other gastrointestinal disorders, but no such guidelines exist for chronic pancreatitis.[4]

Objectives

Objectives of the study were to define the prevalence of bone diseases in patients with chronic pancreatitis by assessing the bone density using DEXA scan and to enumerate the risk factors for bone disease associated in patients with chronic pancreatitis.

METHODS

This single-centre cross-sectional study carried out at Kilpauk medical college from October 2020 to October 2021. This study population consisted of 47 patients who were image confirmed cases of chronic pancreatitis. Informed consent was taken. History of smoking, alcohol use was taken, BMI was measured. All patients were evaluated with an MRCP or CECT within 6 months of study enrolment. BMD was measured at the lumbar spine (mean of first lumbar to fourth lumbar vertebrae), left femur neck. The BMD further corrected in accordance with height of patient. Prevalence of osteoporosis and Osteopenia in patients with chronic pancreatitis was compared to age and gender-matched population derived normative data from Indian population.

Exclusion criteria

History of prolong steroid use, known systemic disease like IBD, chronic liver disease, chronic kidney disease, celiac disease, skeletal disease, malignancy.

Dual-energy X-ray absorptiometry

Bone marrow density (g/cm^2) was calculated for the lumbar spine (L1-L4) and left femoral neck using dual-energy X-ray absorptiometry (Hologic Discovery DXA-scanner) BMD was expressed as T-scores and age-and sex-adjusted Z-scores based on manufacturers reference material. Osteoporosis was defined according to WHO as a T score≤2.5 SD below the young adult mean and osteopenia was defined as a T score between -1.0 SD and -2.5 standard deviation below the young adult mean.[19]

Factors affecting BMD

History was obtained from each patient regarding smoking and alcohol consumption. Alcohol consumption was termed significant if they had consumed at least 4-5 drinks per day for a minimum of 5 years.

Anthropometric assessment

Body weight was measured using a digital electronic weighing scale. Height was measured using a wall-mounted stadiometer. BMI was calculated as measured body weight in kilograms divided by height in meters squared (kg/m^2).

Vitamin D

Quantitative determination of total 25 hydroxy vitamin D was done. (20 ng/ml) was taken as the cut-off for deficiency, those between 20 to 29.9 ng/ml as vitamin D insufficiency and >30 ng/ml was taken as vitamin D sufficiency.

Diabetes

Fasting and post prandial sugars, and HbA1C were measured for all patients by standard technique. Diagnosis of DM was based on American diabetes association (ADA) criteria.[24]

Fecal elastase (FE)

Estimation of pancreatic fecal elastase was done by enzyme-linked immunosorbent assay (ELISA) method using bioserv diagnostics GmbH (Rostock, Germany). Estimation was performed on formed stools only. A value of fecal elastase of >200 mg/g was taken as normal and <100 mg/g as severe exocrine pancreatic insufficiency.

Imaging

All patients who didn't have a CECT abdomen or an MRI abdomen underwent an MRI abdomen with MRCP.

Statistical analysis

Data was entered in Microsoft excel sheet. Statistical analysis was done using SPSS version 20.0 (Statistical packages for social sciences). Chi-square test was done to access the association of variables with the outcome. One-way ANOVA test was done to compare the mean difference of age, BMI, vitamin D levels, duration of chronic pancreatitis, Dexa scan values with the outcomes. P value was considered significant if $p<0.05$.

RESULTS

A total of 47 patients were included. Mean age-45.6 years and 70% (33) were men. Table 1 shows demographics and risk factors for osteoporosis of all patients.

Prevalence of osteoporosis and osteopenia

The prevalence of osteoporosis (combined estimate for femoral neck and lumbar spine) in this patient group was 29.8% in patients with chronic pancreatitis compared to 18.3% in Indian population (p=0.042).

The prevalence of osteoporosis for the femoral neck was 18.5% in CP compared to 7.3% in the Indian population (p=0.058); for the columnar spine, the estimates were 16.9% and 4.7% respectively (p=0.022) (Figure 1). The

prevalence of osteoporosis for the femoral neck (18.5%) comparable to that observed for columnar spine (16.9%) (p=0.82).

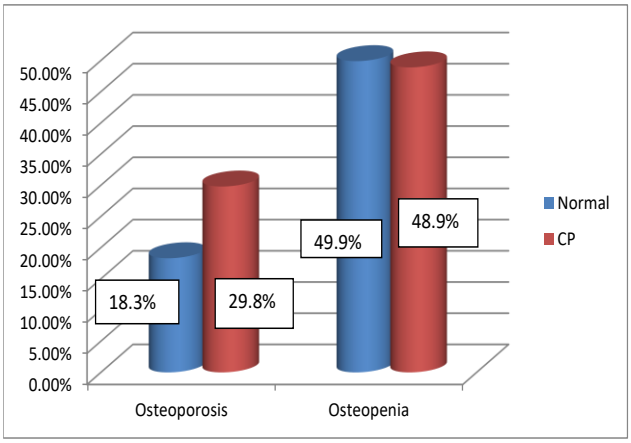

Figure 1: Osteopenia and osteoporosis in study population vs general population.

The prevalence of osteopenia (combined estimate for femoral neck and lumbar spine) 48.9% in patients with chronic pancreatitis; compared to 49.9% in normative Indian population which was not statistically significant.

Risk factors

The mean BMI of the study population was 24.1 kg/m^2, with the mean BMI in patients with osteoporosis was 22.1 kg/m^2, osteopenia was 22.3 kg/m^2 and normal BMD had a mean BMI of 23.5 kg/m^2 which was not statistically significant (p=0.05) as shown in Table 2.

As seen in Table 3, significant alcohol consumption was present in 28 (59.5%) patients, of which 13 patients had osteoporosis and 13 patients had osteopenia. Of the 19 (40.5%) patients without significant alcohol history, 8 patients had normal BMD, 10 had osteopenia and 1 had osteoporosis (p=0.001). Smoking associated as risk factor has been shown in Table 4. History of smoking was present in 19 (40.5%) patients, of which 8 patients had osteoporosis and 11 patients had osteopenia. Of the 28 (59.5%) patients without smoking history, 10 patients had normal BMD, 12 had osteopenia and 6 had osteoporosis (p=0.01).

Table 5 correlates vitamin D levels with bone diseases in these patients. The mean 25 OH vitamin D level of the study population was 24.6 ng/ml. The 24 (51%) patients had a vitamin D levels<20 ng/ml, of which 10 patients had osteoporosis, 13 patients had Osteopenia and 1 patient had a normal BMD. 11(23.4%) patients had a vit D levels between 20-29.9, of which 3 patients had osteoporosis, 07 patients had Osteopenia and 1 patient had a normal BMD. The 12 (25.6%) patients had normal vit D levels, of which 8 patients had normal BMD, 3 had osteopenia and 1 had osteoporosis (p=0.0003).

The 20 (42.5) patients in the study group were found to be/known diabetics, of which 11 patients had osteoporosis, 8 patients had Osteopenia and 1 patient had a normal BMD (p=0.002) as shown in Table 6.

As shown in Table 7, exocrine pancreatic insufficiency was noted in 28 (59.5%) patients, of which 12 patients had osteoporosis, 13 patients had osteopenia and 3 patients had a normal BMD (p=0.02).

Table 1: Demographics and risk factors.

Variables		Cases, (n=47)
Demographics	Age, median (years)	45.6 (18-71)
	Sex, n (%)	Male-33 (70%), female-14 (30%)
	BMI, kg/m^2	23.3
	Duration of chronic pancreatitis, (year)	3.1 (17.3- 32.3)
Risk factors	Alcohol consumption, n (%)	28 (59.9%)
	Smoking, n (%)	19 (40.4)
	Serum 25(OH)-Vitamin-D, ng/ml	24.6 (6.2 -45.9)
	Diabetes, n (%)	20 (42.5%)
	Pancreatic exocrine insufficiency, n (%)	17 (36.1)

Table 2: BMI and outcome.

Variables		Outcome			Total	P value
		Normal	Osteopenia	Osteoporosis		
BMI (Kg/m^2)	<18.5	3	0	0	3	0.05 (NS)
		100%	0%	0%	100%	
	18.5-24.9	4	15	8	27	
		14.8%	55.6%	29.6%	100%	
	25-29.9	3	7	5	15	
		20%	46.7%	33.3%	100%	
	≥30	0	1	1	2	
		0%	50%	50%	100%	
Total		10	23	14	47	
		21.3%	48.9%	29.8%	100%	

Table 3: Alcohol and outcome.

Variables		Outcome			Total	P value
		Normal	Osteopenia	Osteoporosis		
Alcohol	Yes	2	13	13	28	0.001 (S)
		7.1%	46.4%	46.4%	100%	
	No	8	10	1	19	
		42.1%	52.6%	5.3%	100%	
Total		10	23	14	47	
		21.3%	48.9%	29.8%	100%	

Table 4: Smoking and outcome.

Variables		Outcome			Total	P value
		Normal	Osteopenia	Osteoporosis		
Smoking	Yes	0	11	8	19	0.01 (S)
		0%	57.9%	42.1%	100%	
	No	10	12	6	28	
		35.7%	42.9%	21.4%	100%	
Total		10	23	14	47	
		21.3%	48.9%	29.8%	100%	

Table 5: Vitamin D levels and outcome.

Variables		Outcome			Total	P value
		Normal	Osteopenia	Osteoporosis		
Vitamin D levels	<20	1	13	10	24	0.0003 (S)
		4.1%	54.2%	41.7%	100%	
	20-29.9	1	7	3	11	
		9.1%	63.7%	27.2%	100%	
	≥30	8	3	1	12	
		66.7%	25%	8.3%	100%	
Total		10	23	14	47	
		21.2%	48.9%	29.8%	100%	

Table 6: DM and outcome.

Variables		Outcome			Total	P value
		Normal	Osteopenia	Osteoporosis		
DM	Yes	1	8	11	20	0.002 (S)
		5.0%	40%	55%	100%	
	No	9	15	3	27	
		33.3%	55.6%	11.1%	100%	
Total		10	23	14	47	
		21.3%	48.9%	29.8%	100%	

Table 7: EPI insufficiency and outcome.

Variables		Outcome			Total	P value
		Normal	Osteopenia	Osteoporosis		
EPI insufficiency	Yes	3	13	12	28	0.02 (S)
		10.7%	46.4%	42.9%	100%	
	No	7	10	2	19	
		36.9%	52.6%	10.5%	100%	
Total		10	23	14	47	
		21.3%	48.9%	29.8%	100%	

DISCUSSION

We investigated for the prevalence of bone disease in chronic pancreatitis, at our tertiary care centre. The patients had an increased risk of osteoporosis compared to a normative population. Diabetes, EPI, low vitamin-D, alcohol consumption, and smoking were independently associated with decreased BMD. Our findings underline the need for evaluation of bone health in chronic pancreatitis.

Risk factors associated with osteoporosis

Bone disease in chronic pancreatitis can be attributed to several risk factors which act synergistically in propagating abnormal bone metabolism and increase the risk of fractures.

Various causes for reduction in BMD in chronic pancreatitis are: Maldigestion of calcium and vitamin-D, poor dietary intake leading to malnutrition and avoidance of fat-rich meals sitophobia due to steatorrhea related symptoms, chronic inflammation, smoking, alcohol use leading to malnutrition, diabetes mellitus, low sunlight exposure-location, physical limitation, sedentary lifestyle, female gender, increasing age >50 and vitamin-D deficiency.[2]

Prevalence of osteoporosis

We found a more than 1.5 times increased prevalence of osteoporosis in patients compared to the reference population. Overall prevalence of osteopenia and osteoporosis reported in Indian population is 49.9% and 18.3% respectively.[5] Previous studies have reported highly varying prevalence of osteoporosis in chronic pancreatitis ranging from 6.7 to 34%.[3,6-10] These variations maybe because of differences in study populations including different age and gender distributions, as well as differences in aetiology, severity, duration of chronic pancreatitis, and differences in sun exposure.

Risk factors for osteoporosis

Disease duration, alcohol intake, smoking, opioid treatment, EPI, and DM are the main risk factors for undernutrition in adults with chronic pancreatitis.[11-14] Low BMI is an independent risk factor for decreased BMD in the neck of femur, but not in lumbar spine. Similar observations have consistently been reported from observational studies and meta-analyses.[15-20] But our study failed to demonstrate significant association of low BMI with decreased BMD. The pathophysiological

mechanisms underlying these observations have not been fully elucidated, but two mechanisms have been proposed: First, individuals with a high BMI conceivable have more adipose tissue than lean individuals and in adipose tissue aromatization of androgens to oestrogens may contribute to maintaining bone health by maintaining a higher level of oestrogens.[16] Second, physical activity and mechanical loading is essential for maintaining a normal bone health and strength.[21]

Similar to previous studies, our study has also shown a positive correlation between diabetes and BMD in the columnar spine.[22] The pathogenesis of low bone density in type 1 diabetes mellitus (T1DM) is related to decreased peak bone mass because of deficiency in insulin and insulin-like growth factors, leading to slow osteoblast growth and poor collagen synthesis.[23] The interaction, in turn, exists between T2DM and bone health due to several factors, including the direct effects of T2DM on bone metabolism and strength and indirect effects of antidiabetic medication-induced altered bone metabolism.[24]

The mechanism of ethanol associated bone mass is probably multifactorial. Ethanol reduces the BMD due to the inhibition of bone formation.[25-28] Osteoblast releases serum osteocalcin into the circulatory system. At present, osteocalcin is regulated as the most sensitive and specific biochemical marker of osteoblast activity in normal subjects and in patients with metabolic bone disease.[29] Our study also demonstrated an association between chronic alcoholism and low bone marrow density.

Cigarette smoking is a known risk factor for osteoporosis. Numerous studies have documented inverse relationships between smoking and both bone mass and fracture risk.[30,31] It has been suggested that lower bone mass in smokers is attributable to lower body weight rather than any direct effect of tobacco.[30] The effects of smoking on bone mass appear to be dose-dependent, effects of smoking on bone are most pronounced in older individuals several studies of young adults have demonstrated significant effects of smoking on bone mass when analyses are restricted to heavy smokers (>1 pack per day).[32-35] Our study showed a positive correlation of smoking with low BMD.

Similar to other studies, we found that there was a positive correlation between EPI and low vitamin D status. EPI is present in many patients with chronic pancreatitis and in the absence of appropriate enzyme replacement therapy; it may lead to malabsorption of fat and fat-soluble vitamins, including vitamin-D. Vitamin D is an essential hormone for the control of intestinal absorption of calcium and bone mineralization and, as such, vitamin-D deficiency is a well-known risk factor for osteoporosis.[3,36] It seems logical to check chronic pancreatitis patients for fat soluble vitamin deficiencies (A, D, E, and K) whether they have or do not suffer from EPI based on fecal elastase-1 testing. Overall, vitamin-D deficiency seems to be the most common fat-soluble vitamin deficiency, and supplementation should be considered in all patients with chronic pancreatitis.[2] Only 10% of dietary calcium is absorbed in a vitamin D-deficient state, but in the vitamin D-sufficient patient,

calcium intake must also be adequate to prevent loss of BMD. It is suggested that calcium intakes similar to that suggested in celiac disease (1000 mg/d) is warranted in chronic pancreatitis.[36]

Ramsey et al summarized other recommendations for prevention and treatment of bone disease in chronic pancreatitis patients.[37]

Recommendations for prevention and treatment of bone disease in chronic pancreatitis patients- abstain from alcohol and cigarette use, encourage diet high in vitamin-D and calcium, use vitamin-D supplementation, increase weight-bearing physical activity and exposure to sunlight, assess for osteoporosis and osteopenia-DXA every 2 year, if osteopathy, refer to bone specialist for therapy i.e., bisphosphonates and recognize EPI and treat with PERT.

Limitations

The main limitation of the study was its cross-sectional nature, and it was a single centre study, moreover it was performed on a relatively small sample size. Large scale data which are limited in this area, would provide a better insight into the role of bone study in chronic pancreatitis patients.

CONCLUSION

Overall, screening for chronic pancreatitis-associated bone disease, including osteopenia and osteoporosis should be initiated early in the course of chronic pancreatitis even in the absence of EPI, as the overall prevalence of bone disease is approximately two-thirds of chronic pancreatitis patients. We should as well focus on modifiable risk factors such as enzyme replacement therapy in the presence of EPI, maintenance of nutritional state, supplementation of vitamin D and physical activity should be encouraged to preserve muscle function. Bone health management guidelines to be made and strictly needs to be followed in patients with chronic pancreatitis.

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