Original Article

Occult Metabolic Bone Disease in Chronic Pancreatitis

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Abstract

Background: Chronic pancreatitis (CP) leads to malabsorption and metabolic bone disease (MBD). Alcoholic CP (ACP) and tropical CP (TCP) are the two common types of CP. **Objective:** We investigated the presence of occult MBD in patients with CP and compared the same between ACP and TCP. **Materials and Methods:** In this cross-sectional, observational study, we included serial patients of CP in different stages and are grouped as ACP (Group 1; n = 67) and TCP (Group 2; n = 35). We determined serum calcium, phosphorus, alkaline phosphatase, 25-hydroxyvitamin D (25OHD), and intact parathyroid hormone (PTH) levels. Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry in the neck of the left femur. MBD was defined by the presence of either low bone mass (Z-score <−2) or osteomalacia. The results were analyzed using appropriate statistical methods. **Results:** The study participants (85 males; 17 females) had a mean age of 40.8 ± 12.6 years, CP duration of 3.7 ± 4.7 years, and Body Mass Index of 22.5 ± 3.2 kg/m^2. A total of 37 (36%) patients had MBD (osteomalacia in 31 and low bone mass in 6). The frequency of MBD was same in the TCP (16/35) and ACP (21/65) groups (P = 0.1940). Elevated PTH (>70 pg/mL) was seen in 14 patients with 25OHD deficiency and low calcium (<8.5 mg/dL) in 29 patients. BMD did not show a significant correlation with the duration of CP. **Conclusion:** Occult MBD is seen in a third of patients with CP and is similar irrespective of the etiology. The disease is silent and mandates active screening in all susceptible individuals.

Keywords: *Chronic pancreatitis, metabolic bone disease, osteomalacia, osteopenia, osteoporosis*

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Introduction

Chronic pancreatitis (CP) is a systemic disease with a considerable morbidity and mortality.[1] The pancreas has both exocrine and endocrine physiological functions in the body. The loss of exocrine function manifests with malabsorption, and endocrine dysfunction results in diabetes mellitus. The natural course of CP is unclear, and patients may have either exocrine or endocrine dysfunction predominantly.[2] The most common etiologies of the CP include alcohol, gallstone disease, and idiopathic or tropical variety.[3] Tropical calcific pancreatitis (TCP) is characterized by the young age of onset, large intraductal calculi, and a rapidly progressive course toward endocrine and exocrine dysfunction.[4] Previous reports from India have shown regional differences in the spectrum of the clinical manifestations of CP.[5-7] Patients from Northern India showed a higher prevalence of pain and low prevalence of metabolic complications.[5] Pancreatic secretions are essential for the absorption of the fat-soluble vitamins in the body. Vitamin D is an important fat-soluble vitamin that helps in the intestinal absorption of the calcium and plays a major role in the maintenance of skeletal health.[8]

Vitamin D deficiency (VDD) and malabsorption are reported in many gastrointestinal disorders such as

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inflammatory bowel disease, celiac disease, and CP.[9] More than 80% of the apparently normal Indian population were reported to have VDD.[10] In addition to VDD, the skeletal health of CP patients is compromised by malnutrition, general debility, diabetes mellitus, and deficiency of other fat-soluble vitamins. The metabolic bone disease (MBD) in adults has nonspecific symptoms such as easy fatigability, myalgia, and tiredness. Most often, the disease is subtle and manifests in the late stages with an osteoporotic fracture. Indian patients with CP have shown a high prevalence of MBD.[11,12] However, these studies were limited by their geographical distribution and small sample size. Moreover, the differences between the alcoholic CP (ACP) and tropical CP (TCP) have not been evaluated. Hence, we conducted this study to assess the profile of MBD in patients with CP and its relation to the underlying etiology.

Materials and Methods

Study population

We conducted this cross-sectional, observational study at a tertiary-level armed forces referral hospital in India. All patients with a known diagnosis of CP (aged 18–60 years) of any duration under follow-up at our hospital were included in the study. We excluded patients with known thyroid and skeletal disorders, long-term drug intake (glucocorticoids, thyroxine, estrogen, testosterone, and Vitamin D), and the presence of systemic disorders (chronic liver disease, chronic kidney disease, hypogonadism, myeloma, and Cushing's syndrome) that may lead to MBD. We also excluded patients with CP who had steatorrhea and signs of malabsorption suggestive of exocrine deficiency. We excluded patients with exocrine deficiency to minimize the bias of finding a high proportion of patients with MBD in the study population. The patients were divided into two groups based on the etiology for the comparison: Group 1 (ACP) and Group 2 (TCP). All the patients were explained about the aims and objectives of the study and were managed as per the comorbid ailments. The local Ethics Committee approved the trial protocol and all patients provided written informed consent.

Study measures

A fasting blood sample was collected from each participant at 8 a.m., and the serum was analyzed for hematological and biochemical parameters including calcium, phosphorus, alkaline phosphatase (ALP), 25-hydroxyvitamin D (25OHD), and intact parathyroid hormone (PTH). We did not differentiate the data as per the prevailing season and the study was conducted between January 2015 and June 2016. The *T*-score, *Z*-score, bone mineral content (BMC), and bone mineral density (BMD) were assessed by the dual-energy X-ray absorptiometry (DEXA) technique using the Hologic machine (QDR 4500, Hologic® Inc., Waltham, Massachusetts, USA; coefficient of variation, 0.55%). The *T*- and *Z*-scores were calculated on the basis of normal reference values for age- and sex-matched controls from the Indian database provided by the manufacturer of the DEXA machine. The BMD at the neck of left femur was analyzed for the study purpose in all the patients.

Study definitions

CP was diagnosed based on the clinical and imaging criteria.[13] Typically, patients have chronic abdominal pain along with either the presence of pancreatic calcification/atrophy on the ultrasound or the presence of ductal changes on the computed tomography or magnetic resonance imaging. MBD was diagnosed by the presence of either osteomalacia (low 25OHD along with elevated ALP) or low bone mass (*Z*-score <−2 SD) in the patients. We did not use the *T*-score in our study as the majority of the participants were under the age of 50 years. VDD was diagnosed based on the recommendations of the Endocrine Society into sufficiency (>30 ng/ml) and deficiency or insufficiency (<30 ng/ml).[14] The categories of insufficiency and deficiency were not assessed separately due to the small sample size. ACP was diagnosed in a patient with a consumption of more than 14 units/week for 5 years before the onset of CP. TCP was diagnosed after excluding other common causes of CP. The normal radiological appearance of gall bladder and normal gamma-glutamyl transpeptidase value were essential before labeling a diagnosis of TCP. The normal reference ranges for the biochemical parameters in our laboratory were as follows: calcium (8.5–10.5 mg/dL), phosphorus (3.5–5.5 mg/dL), ALP (25–100 U/L), and PTH (15–70 pg/mL).

Statistical analysis

Data are presented as mean ± S.D and a comparison between the groups was done using nonparametric (Mann-Whitney U-test) and Fisher's exact tests. Pearson's correlation test was used for correlation between normally distributed continuous variables, and $P < 0.05$ was considered statistically significant. The statistical analysis and graph generation was done using the GraphPad Prism Software, Version 6 (GraphPad Software, San Diego, CA, USA).

Results

The study consists of 85 males and 17 females with a mean age of 40.8 ± 12.6 years, CP duration 3.7 ± 4.7 years, body weight 63.3 ± 10.8 kg, and Body Mass Index 22.5 ± 3.2 kg/m^2. A total of 67 patients had ACP and the remaining 35 had TCP. Pancreatogenic diabetes mellitus was seen in 54 patients with average

Table 1: Comparison of parameters between the two groups of chronic pancreatitis

Feature	Units	Group 1 (alcoholic CP) *n*=67	Group 2 (TCP) *n*=35	*P*
Demographic parameters				
Age	Years	40.4 (11.8)*	41.4 (14.2)	0.7114
Sex	Male:female	67:0	18:17	<0.0001
Duration of CP	Years	3.2 (3.2)	4.4 (6.7)	0.2233
Body weight	kg	64.6 (10.4)	60.8 (11.1)	0.0927
BMI	kg/m^2	22.4 (3.2)	22.8 (3.3)	0.4849
Biochemical parameters				
Calcium	mg/dL	8.8 (0.76)	8.9 (0.71)	0.7060
Phosphorus	mg/dL	3.5 (0.69)	3.7 (0.71)	0.1656
ALP	U/L	92.3 (34)	107.6 (52.9)	0.0795
25OHD	ng/mL	26.6 (18.6)	33.9 (28.8)	0.1232
Intact PTH	pg/mL	40 (30.9)	49.8 (35.2)	0.1527
Bone density parameters				
BMC	g/cm^2	1.17 (0.13)	1.05 (0.14)	<0.0001
T-score	Number	−0.29 (0.97)	−0.53 (0.99)	0.2402
Z-score	Number	−0.26 (0.94)	−0.51 (1/02)	0.2263
Z-score <−2	*N* (%)	3 (5)	3 (9)	0.4103
Z-score between −1 and−2	*N* (%)	14 (21)	7 (20)	1.0000
Z-score >−1	*N* (%)	50 (74)	25 (71)	0.8142
Osteomalacia (↓25OHD and↑ALP)	*N* (%)	18 (27)	13 (37)	0.3650

*Mean (SD). SD=Standard deviation; BMI=Body mass index; CP=Chronic pancreatitis; TCP=Tropical chronic pancreatitis; 25OHD=25-hydroxyvitamin D; ALP=Alkaline phosphatase; PTH=Parathyroid hormone; BMC=Bone mineral content

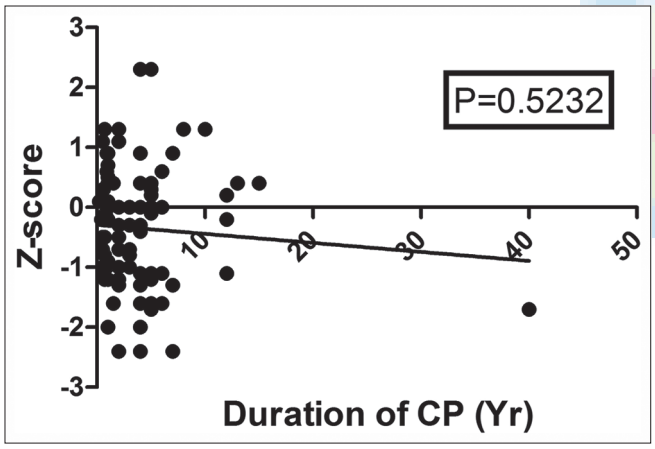

Figure 1: Correlation between duration of chronic pancreatitis and bone mineral density

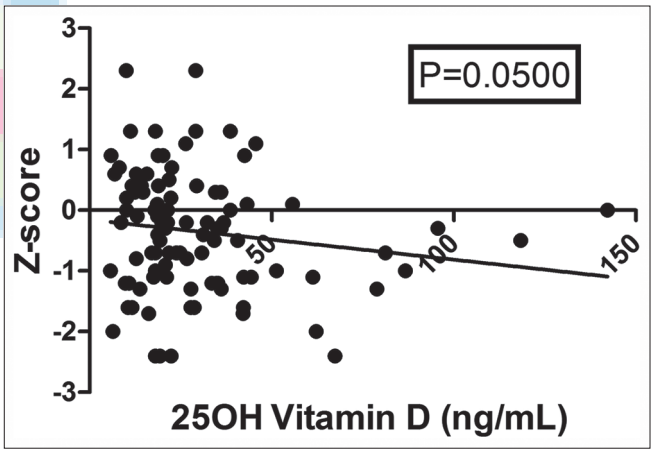

Figure 2: Correlation between 25-hydroxyvitamin D and bone mineral density

glycosylated hemoglobin of 7.5 ± 1.6%. A total of 69 patients had 25OHD deficiency, of them 31 patients had elevated ALP. Low bone mass was seen in 6 patients and 21 patients had BMD *Z*-score between −1 and −2. Hence, MBD was seen in 37 patients (36%) with CP (osteomalacia –31 and low bone mass – 6). The BMD was normal in the remaining 75 patients.

Elevated PTH (>70 pg/mL) was seen in 14 patients with 25OHD deficiency. Serum calcium was low (<8.5 mg/dL) in 29 patients and the remaining had normal calcium values. The details about the patients in both groups are given in Table 1. Briefly, there were no significant differences between the MBD as per the underlying etiology of CP except for BMC. We did univariate correlation analyses between the BMD and other important parameters. BMD did not show a significant correlation with the duration of CP [Figure 1]. The levels of 25OHD showed a trend toward negative correlation with the BMD level as shown in Figure 2. We did not perform multivariate correlation analyses due to the small sample size in our study.

Discussion

Our study showed that occult MBD was seen in one-third of patients with CP. Previous reports from India showed that the prevalence of MBD was more than 70%

in patients with CP (5–7, 11, and 12). The exclusion of patients with exocrine dysfunction could explain the low prevalence in our study. Another contributing factor is the fact that all our patients belong to the armed forces, who have a better living standards in comparison to the general population. Previous reports from the developed countries have shown that the prevalence of MBD was 39% in patients with CP, similar to the finding observed in our study.[15,16] In our study, the majority of the patients had osteomalacia followed by low bone mass. Previous reports from our country showed a similar distribution of MBD. Joshi *et al*. showed low bone density (*Z*-score <−2) in 22 of 72 patients and Sudeep *et al*. study showed similar findings in 9 of 31 (*T*-score <−2.5) patients.[5,11] We did not include the term osteoporosis as the same had not been validated in younger population.

Our data showed that the prevalence of the MBD was same irrespective of the underlying etiology and the presence of diabetes. Systemic inflammation plays a major role in the bone loss rather than the underlying etiology of CP.[11,12,17] However, they have used the term "osteoporosis" in a group of patients with a mean age of <40 years, which could have confounded the results.[12] Another study showed that changes in the BMD are observed even in patients with normal exocrine function.[9] This suggests that early screening is essential to identify the occult MBD abnormalities in these patients.

The exocrine function of the pancreas is preserved till 90% of the gland is atrophic. Hence, MBD is seen more commonly in patients with advanced stages of the CP.[17] However, our data did not show a correlation between the duration of CP and the loss of bone as shown in Figure 1. The majority of the participants had <2 years' duration of CP, thereby explaining the lack of association. Our data also showed that the BMD did not correlate with the level of 25OHD. A study from South India also showed similar finding and suggested that long-standing malabsorption could be the cause of the loss of BMD rather than VDD.[11] Sudeep *et al*. also showed that the duration of diabetes had no influence on the prevalence of MBD.[11]

VDD was seen in 70% of patients in our study, which is similar to other reports from India.[5,12] Sudeep *et al*. have shown that 71% of their patients had VDD, whereas another study from the Central India showed VDD in 86% of the patients.[5,11] Another interesting observation of our study is the finding of negative correlation between the BMD and 25OHD level as shown in Figure 1. This discrepancy could be explained by the known effect of hypervitaminosis D in increasing bone resorption and a reduction in the BMD.[18] Another possibility could be the discrete Vitamin D replacement by the patients without informing the same during the interviews.

The strength of our study includes assessment of BMD using the DEXA technique which is the best for the diagnosis and the use of *Z*-score instead of *T*-score. The limitations of our study include small sample size, failure to measure urine calcium excretion, and lack of the control group. The cross-sectional nature of our study limits the usefulness in predicting the cause-and-effect relation between CP and MBD.

Conclusion

Occult MBD is common in patients with CP and the prevalence is similar irrespective of the underlying etiology. It is essential to screen for the presence of VDD and MBD in all patients with CP. Further large-scale studies with more number of patients are required to confirm the findings observed in our study.

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Conflicts of interest

The authors declared that they have no conflicts of interest.

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