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Research Article

TO STUDY THE PREVELANCE OF VITAMIN D DEFICENCY IN CHRONIC PANCREATITIS AND IT'S CORRELATION WITH SEVERITY OF THE DISEASE

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A B S T R A C T

Background: Chronic pancreatitis (CP) is a result of progressive and irreversible damage of the pancreas. This process leads to progressive loss of pancreatic exocrine and endocrine function. Pancreatic exocrine insufficiency following chronic pancreatitis can cause or worsen an existing vitamin D deficiency.

Objective: In this study, we aim to determine the prevalence of vitamin D deficiency among chronic pancreatitis patients. We also intend to determine the correlation of vitamin D deficiency with the severity of disease as classified by modified Cambridge classification.

Methods: The study was conducted in patients admitted in Medical Gastroenterology department, Madras Medical College, RGGGH from January 2018 to December 2018. Newly diagnosed chronic pancreatitis were included in the study. Clinical history and baseline evaluation (biochemical and imaging) was done for all the patients. Severity was assessed by modified Cambridge scoring system. Determination of 25-hydroxyvitamin D (25 OH D, the amount of 25OHD3 and 25OHD2) is committed by certified ID-LC-MS method (Liquid chromatography-tandem mass spectrometry) with accuracy and precision within 7.5% and linearity range 3.0-300.0nmol/L. Levels of 25OHD below 25nmol/L were defined as deficiency, 25-50nmol/L- as severe insufficiency, 50-75 nmol/L - mild insufficiency and above 75 nmol/L - as normal, or without insufficiency.

Results: Study encompassed 140 patients in two subgroups: 108 patients with proven CP (52% males; group mean-aged 52.7 years) and 38 matched control subjects (43% males, mean-aged 54.2 yrs) who consented to participate. Vitamin D (25OHD) levels in CP patients were found lower than in the control subjects(p 0.036). Absolute 25OHD deficiency (values under 25nmol/L) was observed in 37.5% (41) of patients with CP, while the absence of deficiency (25OHD >75 nmol/L) was found only in 8.3% (8) patients. The mean 25OHD levels were found lower in patients who were associated with diabetes. We found a difference between 25OHD mean values for subgroups 1- 4 by CT/MRCP ($p<0.001$). Patients with less severe CP assessed by means of CT/MRCP had lowest incidence of vitamin D deficiency. Also, no deficiency was only found in 4 patients Cambridge 1 and 2 patients Cambridge 2 (5.6% and 2.8% respectively). Between the subgroups of mild (Cambridge 1 and 2) and severe structural changes (Cambridge 3 and 4) there was also a statistically significant difference, $p <0.0001$.

Conclusion: Most of our CP patients were with vitamin D deficiency and insufficiency and there was a strong relationship between 25OHD levels and severity of morphological imaging data with increased risk for 25OHD deficiency. Therefore, vitamin D assessment should be done in all cases of pancreatitis and should be supplemented accordingly.

INTRODUCTION

The traditional definition of chronic pancreatitis has been based on histology, with features of chronic and irreversible damage to the pancreas. These features include chronic inflammation, fibrosis, and eventual destruction of ductal, exocrine (acinar cell) and endocrine (islets of Langerhans) tissue producing varying degrees of symptoms and structural and functional derangements of the gland[1]. Deficiencies of fat-soluble vitamins may develop in patients with chronic pancreatitis and steatorrhea. Significant vitamin D deficiency and osteopenia or even osteoporosis occur in patients with chronic pancreatitis [13]. These studies demonstrate osteopenia in 50% to 70% and osteoporosis in up to 20% of patients with chronic pancreatitis and steatorrhea [6]. In the literature, there are only very few articles focussing on this

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topic. Most of them report on single observations or small groups of patients. The results differ to some extent, some authors report normal serum 25(OH)D concentrations, some on reduced levels in pancreatic patients, to some extent also in correlation to decreased levels of pancreatic elastase in the stool as an indicator of exocrine pancreatic insufficiency

Current approach to the diagnosis of CP is based on a set of imaging and functional tests. The criteria for diagnosing chronic pancreatitis in adults using different imaging techniques should be applied according to the Cambridge classification.The Cambridge classification based on ERCP and its adaptation (table 1) for sectional imaging (ultrasound, EUS, CT/MRCP) should be used for diagnosing chronic pancreatitis in adults.

Table 1 Adaptation of Cambridge Criteria for CT/MRCP

Cambridge 0	Normal pancreas
Cambridge 1	Not possible to diagnose on CT/MRCP using current methods
Cambridge 2	Two or more of the following pathological changes: Pancreatic duct between 2 and 4 mm in the pancreatic body Mild pancreatic enlargement Heterogeneous parenchymal structure Small cystic changes (<10 mm) Duct irregularities Pathological side branches >3
Cambridge 3	All changes listed under 2 plus pathological main duct (>4 mm)
Cambridge 4	One of the changes listed under 2 or 3 plus one or more of the following: Cystic structures >10 mm Parenchymal calcifications Intraductal filling defects (calcifications) Duct obstruction (strictures)Major duct irregularities

Therefore we started a prospective study into the rate and extent of reduced serum 25(OH)D concentrations in patients suffering from chronic pancreatitis and it's correlation to severity as per modified Cambridge classification.

Aim

In this study, we aim to determine the prevalence of vitamin D deficiency among chronic pancreatitis patients. We also intend to determine the correlation of vitamin D deficiency with the severity of disease as classified by modified Cambridge classification.

METHODOLOGY

The study was conducted in patients admitted in Medical Gastroenterology department, Madras Medical College, RGGGH from June 2018 to December 2018. Newly diagnosed chronic pancreatitis were included in the study. Clinical history and baseline evaluation (biochemical and imaging) was done for all the patients. Severity was assessed by modified Cambridge scoring system. Determination of 25-hydroxyvitamin D (25 OH D, the amount of 25OHD3 and 25OHD2) is committed by certified ID-LC-MS method (Liquid chromatography-tandem mass spectrometry) with accuracy and precision within 7.5% and linearity range 3.0-300.0nmol/L. Levels of 25OHD below 25nmol/L were defined as deficiency, 25-50nmol/L- as severe insufficiency, 50-75 nmol/L - mild insufficiency and above 75 nmol/L - as normal, or without insufficiency.

Statistics

Data were entered in Microsoft Excel and analysed using IBM SPSS Software Version 20.0. Percentage analysis was used for categorical variables. Mean with Standard Deviation or Median with Inter-quartile range (IQR) were used for continuous variables depends on the normal distribution. Comparison of Parametric Data and Non Parametric data between two groups were done by using Student's t test (Unpaired t test) and Mann-Whitney U test respectively. Comparison of categorical variable between the group was done by using Chi-Square test. Discriminatory performance of variables was determined by area under the receiver operating characteristic (ROC) curve, and best cut-off values were calculated based on operating characteristic (ROC) curve, and best cut-off values were calculated based on the High Sensitivity and Specificity. A p value of < 0.05 was considered statistical significance with 95% Confidence Interval.

RESULTS

This study enrolled 140 patients, of which 32 were control and 108 were diagnosed to have chronic pancreatitis on basis of clinical and radiological evidence. Mean levels of 25OHD for the whole group were 41.53 ± 26.14 nmol/L (range 5.8- 84.7). Vitamin D levels in CP patients were found lower than in the control subjects: 38.34 ± 25.04 as compared to 52.45 ± 27.65 nmol/L(p=0.036). Absolute 25OHD deficiency (< 25 nmol/L) was found in 41 (37.5%) patients with CP whereas profound insufficiency (25–49.9nmol/L) was found in 32 (29.2%) patients and mild insufficiency (50–79.9nmol/L) was found in 27 (25%) patients. Normal vitamin D (25OHD>80 nmol/L) was found only in 9(8.33%) patients.

Table 2 Serum vitamin D levels stratified by etiologic and clinical characteristics of patients with CP

Charecteristic		n	Mean±SD	95% CI	p value
Age	<50y	54	40.89±25.1 6	32.38- 9.40	0.5 97
	>50	54	37.97±27.3 5	28.72- 7.23	
Gender	male	59	44.59±27.5 5	44.59±27.5 5	0.o7
	female	49	33.34±23.3 1	25.07- 1.60	
Alcohol	no	51	42.27±26.6 1	32.98- 1.56	0.098
	yes	57	36.89±25.7 8	28.42- 5.37	
Smoking	no	50	48.14±26.9 1	38.59- 7.68	0.011
	yes	58	32.07±23.3 4	24.5- 39.63	
Weight loss	no	62	40.99±25.8 4	32.84- 9.15	0.491
	yes	46	37.36±26.8 0	27.54- 7.19	
Diabetes	no	81	43.54±26.7 5	36.24- 0.84	0.026
	yes	27	27.09±20.1 7	17.07- 7.12	

Lower vitamin D was observed in women and alcohol consumer (p>0.05). The mean vitamin D levels were found lower in smokers (vs non-smokers) and patients with diabetes (vs non-diabetic) (table 2, p<0.05 for all comparisons t-test).

No deficiency (vitamin D above 80 nmol/l) was only found in 6 patients with Cambridge 1 and 3 patients Cambridge 2 classification (5.6% and 2.8% respectively). Patients with less severe CP had lowest incidence of vitamin D deficiency.

Table 3 Results for mean 25OHD values within the different CT / MRCP groups

CT/MRCP	n	25OHD Mean±SD	95% CI
Cambridge 1	27	57.96±25.34	45.30-72.49
Cambridge 2	28	46.94±22.35	36.64-59.07
Cambridge 3	26	29.24±19.40	18.81-37.85
Cambridge 4	27	24.44±21.06	13.77-33.30
All		38.52±27.24	33.29-45.57

More severe the structural changes, more was severe is the vitamin D deficiency. The lowest levels of 25OHD were observed in patients with severe structural changes Cambridge 3 and 4 as compared to less severe structural changes Cambridge 1 and 2. There was a significant difference between

25OHD mean values for subgroups 1- 4 as assessed by CT/MRCP(p <0.001). Between the subgroups of mild (Cambridge 1 and 2) and severe structural changes (Cambridge 3 and 4) there was also a statistically significant difference (p <0.0001).

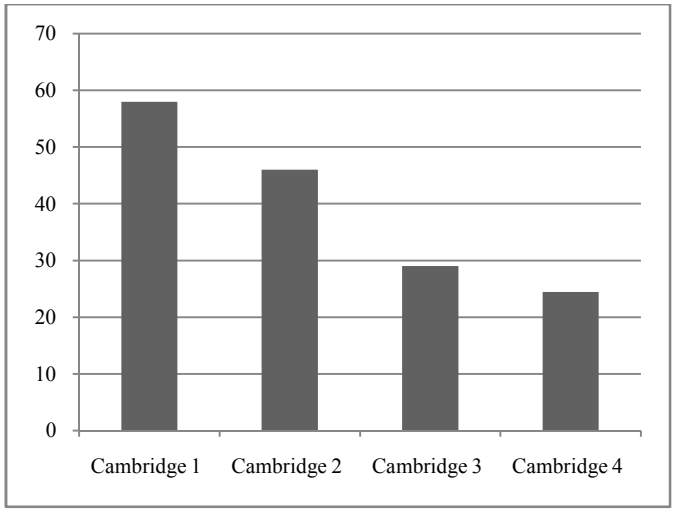

Figure 1 Mean vitamin D levels for Cambridge subgroups

DISCUSSION

The prevalence of vitamin D deficiency in the studied population was 59.2% with cut-off for vitamin D levels below 50nmol/L. The community-based Indian studies of the past decade done on apparently healthy controls reported a prevalence ranging from 50% to 94%, except for one study which reported a prevalence of 34.5% which can be due to the low cutoff.]. A study conducted amongst Indian postmenopausal women to evaluate their dietary calcium and vitamin D status documented that, 18% subjects had normal 25(OH)D levels, 52% subjects had 25(OH)D insufficiency, and 30% subjects had 25(OH)D deficiency. Another study carried out on school and college students aged 16-60 year demonstrated that the mean serum 25(OH)D value of study subjects was 17·5 nmol/l; 87% (95% CI 84·5, 89·6) of the subjects had 25(OH)D ≤ 25 nmol/l confirming the earlier reports of wide prevalence of hypovitaminosis D in apparently healthy Asian Indians[6,7,18]. In the patients with CP we observed higher rate of absolute deficiency with levels below 25nmol/L in 37.5% patients while no insufficiency were detected only in 8.33%. In regard to the 25OHD deficiency distribution among CP patients our results were similar as compared with the published data. Duggan S. *et al*[2,3,4] find 25OHD deficiency rate 58% and Sikkens E. *et al* [15] 53%. Studies among Asian population describe higher prevalence for 25OHD deficiency. Joshi *et al* [7]demonstrated that 86% of patients with tropical calcific pancreatitis were deficient. Most of the published studies are actually based on case-series and only few of them are case-control studies. The differences in the vitamin D deficiency distribution based on the type of studies are significant. We have found relationship between levels of 25OHD and CT/MRCP severity grade, Diabetes and smoking. Main risk factor is severe CT/MRCP changes Cambridge 3 and 4 similarly to results of Mann *et al*[10]. In our study diabetes and PEI contributed less to the development of a 25OHD deficiency than severe CT/MRCP changes. Besides malabsorption other factors may influence the 25OHD deficiency. The chronic pain which is associated with malnutrition due to a poor food intake. In addition chronic pancreatitis patients tend to avoid fat meals fearingsteatorrhea-related symptoms. Other important contributing factor is chronic inflammation and inflammatory mediators, related protein-energy malnutrition and consequent bone mineral loss.

CONCLUSION

In patients with chronic pancreatitis and severe structural changes prevails low vitamin D levels regardless of age and sex. Diabetes and smoking can be additional contributing factors. These data imply the necessity of precise assessment of vitamin D deficiency in patients with chronic pancreatitis regardless of the loss of pancreatic function. Screening for vitamin D deficiency is an important integral part of the evaluation of PEI and nutritional status in chronic pancreatitis.

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