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Vitamin D Deficiency In Chronic Pancreatitis

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Abstract: ***The main objective of this study was to determine the prevalence of 25OHD deficiency in patients with chronic CP, and to assess its relations to the contributing factors. Study encompassed 93 patients in two subgroups: 72 patients with proven CP (52% males; group mean-aged 52.7 years) and 21 matched control subjects (43% males, mean-aged 54.2 yrs) who consented to participate. CP patients were subdivided according to Cambridge classification for CT/MRCP (grade 1–4). 25-Hydroxyvitamin D (25OHD, sum of $25OHD_3$ and $25OHD_2$) was analyzed by a ID-LC-MS/MS method. Results: 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% (27) of patients with CP, while the absence of deficiency (25OHD >80nmol/L) was found only in 8.3% (6). The mean 25OHD levels were found lower in patients with diabetes (vs non-diabetic) and those presented with Pancreatic Exocrine Insufficiency, p<0.05. We found a difference between 25OHD mean values for subgroups 1- 4 by CT/MRCP, p<0.001. Seasonal difference in 25OHD status was significant for patients with Cambridge 1 and 2 grade (mild changes) and in the control subjects. In the opposite, the lowest 25OHD levels were registered for patients with severe imaging data Cambridge 3 and 4, without effect of season; p<0.005, odd Ratio 10.37. 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.***

Key words: Chronic pancreatitis, Vitamin D, 25OHD, Vitamin D deficiency, PEI

Introduction

Chronic pancreatitis (CP) is a result of progressive and irreversible damage of the pancreas. Most commonly it develops after recurrent inflammatory episodes and consequent replacement of normal pancreatic parenchyma with fibrous tissue. This process leads to progressive loss of pancreatic exocrine and endocrine function. Current approach to the diagnosis of CP is based on a set of imaging and functional tests. [8,10] Resent nutritional research in chronic pancreatitis demonstrated a link between fat-soluble vitamins deficiency and increased risk of osteoporosis[5]. Dietary intake provides between 10 and 20% of the required amount for the body, but inadequate vitamin D status with proven deficiency is established in most populations, especially those in the far northern or southern latitudes[13]. PEI following various pancreatic diseases can cause or worsen an existing vitamin D deficiency. Published studies on the 25OHD deficiency are heterogeneous and not all of them report the PEI presence, pancreatic surgery and endocrine insufficiency. We aimed to measure vitamin D levels in Bulgarian patients with chronic pancreatitis of various aetiology in order to

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determine the prevalence of 25OHD deficiency and assess it relations to the contributing factors.

Materials and Methods

Patients and diagnosis: we have prospectively studied 72 patients with chronic pancreatitis and 21 control subjects without signs, symptoms or imaging suggestive of chronic pancreatitis between March 2014 to February 2016. Among CP patients 52% were males and 48% females; mean aged 52.7 ± 13.7 years (range 22 - 84 yrs). The matched control subjects were 43% males, mean-aged 54.2 yrs (range 22 - 79yrs), p=ns. All participants were admitted and/or followed up in the Gastroenterology department of University Hospital "Tsaritsa Ioanna-ISUL" after obtaining of informed consent in accordance with the Declaration of Helsinki, its amendments and the GCP principles. The clinical signs and symptoms were assessed by gastroenterologist. CP diagnosis is made on accepted M-ANNHEIM criteria [19]. NOne of the patients were on Vitamin D supplementation at the time of sampling and assessment. Criteria for alcohol abuse was SRAI 25 – 900 g/day and for smoker 5 to 70 pack-years.

Pancreatic morphology: Initially all subjects underwent abdominal ultrasound and structural changes were confirmed either by CT or MRCP (using Cambridge classification[10,18]). Disease staging is performed and documented by radiologist.

Vitamin D (25 hydroxy vitamin D): Determination of 25-hydroxyvitamin D (25 OH D, the amount of 25OHD3 and 25OHD2) is committed by a validated DEQAS(Danish External Quality assessment scheme) certified ID-LC-MS / 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, 50-80 nmol/L - mild insufficiency and above 80 nmol/L - as normal, or without insufficiency.

PEI: Presence of PEI was confirmed by measurement of Fecal Elastase-1 (FE-1) by enzyme immunoassay (ELISA) with specific monoclonal antibodies (ScheBo® Biotech FE-1 ELISA Germany). The generally accepted cut off is 200 μg/g feces and levels below it were indicative for PEI.

Statistical methods: Statistical analysis was performed using SPSS 21.0 (Chicago, IL). The data were described by the mean, 95% confidence interval (CI) of the mean, standard deviation (SD) and standard error of the mean (SEM), presented in graphical and tabular form. Normality of distribution was assessed by Kolmogorov-Smirnov and Shapiro-Wilk tests. Alpha level of 0.05 was accepted as significant.

Results

We have enrolled 93 subjects, of which 72 patients diagnosed with chronic pancreatitis and 21 control individuals without signs of pancreatitis. Mean levels of 25OHD for the whole group were 42.62 ± 27.23nmol/L (range 3.8-105.7). Vitamin D levels in CP patients were found lower than in the control subjects: 39.43 ± 26.13, versus 53.54 ± 28.74nmol/L, p=0.036. Absolute 25OHD deficiency with values under 25 nmol/L was observed in 37.5% (27) of patients with CP, profound insufficiency (25–49.9nmol/L) was found in 29.2% of patients(21); within the range 50–79.9nmol/L assessed as mild insufficiency were 25%(18), while the absence of deficiency (25OHD>80 nmol/L) was found only in 8.33% (6). Table 1 shows serum vitamin D levels stratified by demographic, etiologic and clinical characteristics of patients with CP. There is a trend for lower level of vitamin D in women, patients with alcohol abuse and weight loss, p>0.05. The mean vitamin D levels were found lower in smokers (vs non-smokers), patients with diabetes (vs non-diabetic) and those presented with PEI (table 1, p<0.05 for all comparisons t-test). In the subgroup of CP patients we observed a clear trend to higher vitamin D levels in those

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who were assessed during the summer (May to October) with a peak in July and August and lower values during the winter season (November-April), lowest in January and February (p 0.006).

	25OHD	n	Mean±SD	95% CI	*p
Age	<50y	36	40.89±25.16	32.38-9.40	0.597
	>50y	36	37.97±27.35	28.72-7.23	
Gender	male	39	44.59±27.55	35.66-3.52	0.073
	female	33	33.34±23.31	25.07-1.60	
Season	winter	26	27.87±20.81	19.46-6.27	0.006
	summer	46	45.97±26.76	38.02-3.91	
Alcohol	no	34	42.27±26.61	32.98-1.56	0.398
	yes	38	36.89±25.78	28.42-5.37	
Smoking	no	33	48.14±26.91	38.59-7.68	0.011
	yes	39	32.07±23.34	24.5-39.63	
Weight loss	no	41	40.99±25.84	32.84-9.15	0.491
	yes	31	37.36±26.80	27.54-7.19	
Diabetes	no	54	43.54±26.75	36.24-0.84	0.026
	yes	18	27.09±20.17	17.07-7.12	
PEI	Yes	36	33.00±23.69	24.98-1.02	0.043
	No	36	45.86±27.18	36.67-5.06	
Therapy EST	no	42	39.09±27.74	30.44-7.73	0.648
	yes	30	39.91±24.16	30.89-8.94	

Table 1 (t-test and Mann-Whitney depending on distribution)

Control group showed a similar trend, with higher vitamin D values (mean 66.02 ± 25.69nmol/L) measured in summer than in winter (39.81 ± 26.48nmol/L), p = 0.036. Interestingly, when compared CP patients and control groups mean values distributed by seasons we found: for summer chronic pancreatitis / summer controls , p = 0.041, but no statistically significant difference between winter CP / winter controls, p = 0.16. Similarly there is no significant difference between summer values in CP and winter values in the control group (p = 0.38, Mann-Whitney)

Vitamin D and pancreatic morphological changes

Patients with less severe CP assessed by means of CT/MRCP had lowest incidence of vitamin D deficiency. Also, no deficiency (vitamin D above 80 nmol/l) was only found in 4 patients Cambridge 1 and 2 patients Cambridge 2 (5.6% and 2.8% respectively), figure 1. The results for mean 25OHD values within the different CT / MRCP groups are presented in table 2:

CT/MRCP	n	25OHD Mean±SD	95% CI
Cambridge 1	17	58.89±26.44	45.30-72.49
Cambridge 2	19	47.85±23.26	36.64-59.07
Cambridge 3	17	28.33±18.51	18.81-37.85
Cambridge 4	19	23.53±20.26	13.77-33.30
All	72	39.43±26.13	33.29-45.57

Table2(ANOVA)

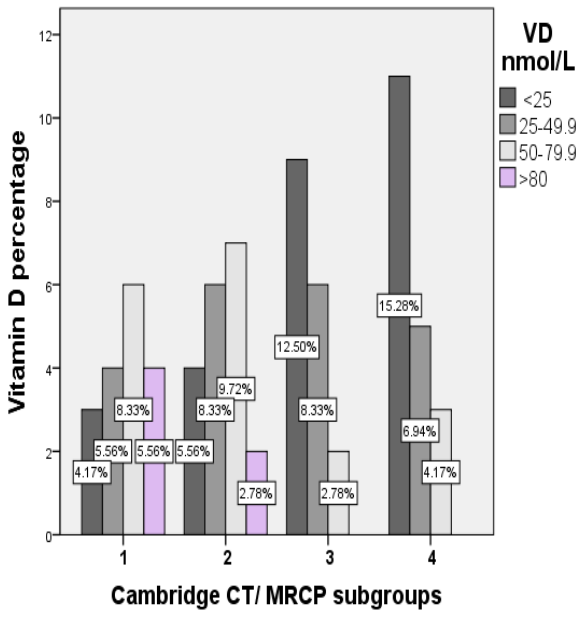

Figure 1 Percentage distribution of patient outcomes in subgroups by morphological severity and criteria for vitamin D deficiency / insufficiency

The lowest levels of 25OHD were observed in patients with severe structural changes Cambridge

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3 and 4. We found a significant difference between 25OHD mean values for subgroups 1- 4 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 . These data are presented graphically in Figure 2.

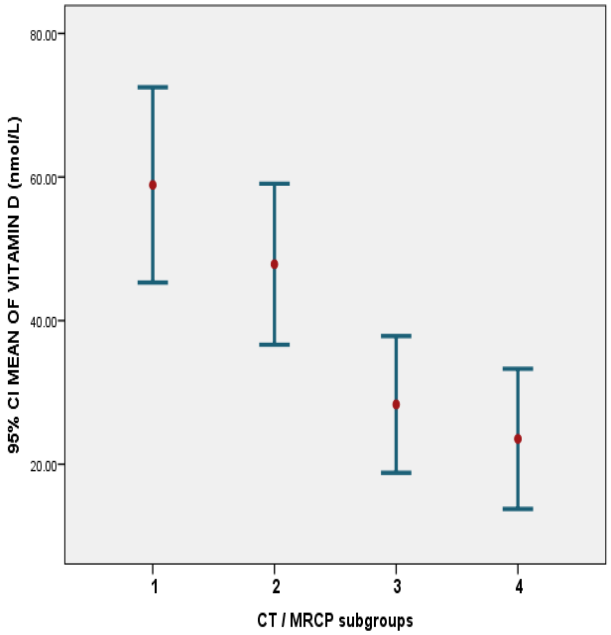

Figure 2 Mean vitamin D levels for Cambridge subgroups

In order to assess the impact of period of sampling to the results, patients diagnosed with CP are distributed to mild (Cambridge 1 and 2) and severe (Cambridge 3 and 4) morphological changes and accordingly the time of sampling summer/winter into four subgroups. Data are presented in Table 3. There is no differences in patients with chronic pancreatitis with severe structural changes (subgroups 3 and 4 CT / MRCP) studied in winter and in the summer. The levels of vitamin D are low regardless of the season of sampling. Winter and summer mean 25OHD levels for control group were compared to the mean levels for Bulgarian population[2] Winter-Spring (27.14-43.56nmol/L) and Summer-Autumn (67.14-52.54nmol/L). No differences were found, (p<0.05, One sample t-test).

	N	Mean± SD	95% CI	p
Winter / Cambridge 3 and 4	15	25.30±21.16	13.58-37.02	0.68
Summer / Cambridge 3 and 4	21	26.15±18.44	17.76-34.55	
Winter / Cambridge 1 and2	11	31.37±20.78	17.41-45.33	0.00 01
Summer / Cambridge 1 and2	25	62.61±20.66	54.08-71.14	
Winter controls	10	39.81±26.48	20.86-58.75	0.03 6
Summer controls	11	66.02±25.70	48.76-83.29	
Total	93	42.62±27.23	37.01-48.23	

Table 3 Seasonal distribution of sampling in different subgroups by severity of CP and control group.

In order to investigate main factors contributing to 25OHD deficiency rate we performed multiple logistic regression analysis using Backward stepwise method at 25OHD value of 50nmol/L and 25OHD predictors: CT/MRCP grades, season groups (Summer/Winter), calcifications, Diabetes and PEI presence.

We have found that significant factors were CT/MRCP grade (p=0.032) and seasonal influence. Severe morphological grades 3 and 4 were with the highest risk for 25OHD deficiency (p 0.025, Odd Ratio, OR 10.37, 95%CI 1.34-80.39). However the effect of the seasonal influence was only 16% (OR 0.160, with 95%CI 0.048-0.529, p =0.003) on the 25OHD levels. PEI was not a contributing factor for developing of deficiency in the studied group (OR 1.64, 95%CI 0.44-6.18, p=0.46). Diabetes and calcifications on the imaging were also not significant risk factors (p 0.084 and 0.20 respectively).

Discussion

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The prevalence of vitamin D deficiency in the studied population was 59.2% with cut-off for vitamin D levels below 50nmol/L. In the subgroup of patients with PEI we have found deficiency in 27 (74%) of patients, which is higher when compared with the prevalence of deficiency in the whole group. Previously published cohort study on vitamin D levels in Bulgarian general population showed that 21% of participants had levels less than 25nmol/L and 24% - levels above 80nmol/L. 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 [3] find 25OHD deficiency rate 58% and Sikkens E. et al - 53% [20]. Studies among Asian population describe higher prevalence for 25OHD deficiency. Joshi et al demonstrated that 86% of patients with tropical calcific pancreatitis [12] were deficient. Most of the published studies are actually based on case-series and only few of them are case-control studies[3,12,14]. The differences in the vitamin D deficiency distribution based on the type of studies are significant. Those, which included more patients presented with PEI, showed higher levels of deficiency.[12]

We have found relationship between levels of 25OHD and CT/MRCP severity grade, PEI, Diabetes presence and smoking. Main risk factor is severe CT/MRCP changes Cambridge 3 and 4 similarly to results of Mann et al.[15] They determined severity of CP by ERCP and FE-1 in 42 chronic pancreatitis male patients and observed a significant correlation between increasing severity of disease and decreased vitamin D levels. On the opposite, other authors did not find such a relation, [3,17]. In our study diabetes and PEI contributed less to the development of a 25OHD deficiency than severe CT/MRCP changes. When discussing the PEI, which we have diagnosed by measuring FE-1, we have to mention the limitations of the all indirect tests for detecting PEI discussed elsewhere. However, the most of the resent guidelines [8,10] recommend FE-1 level of 200 µg/feces as a reliable tests for the diagnosis of PEI in the routine clinical practice. We did not found any association between enzyme substitution therapy (EST) and 25OHD levels supporting the results, previously published by Sikkens E. et al and Dutta et al [7,20], who also demonstrated that deficiencies of fat soluble vitamins are present regardless to EST.

The limitations of our study include the relatively short period of observation and lack of assessment of the bone mineral density, as osteoporosis is one of the most serious consequences of 25OHD deficiency. Some of the published data on the osteoporosis/osteopenia among CP patients shows osteopenia in 26%, and osteoporosis in 5% in patients with pancreatitis[6]. Other authors describe a relationship between steatorrhea in patients with severe CP and advanced bone loss[16]. Sudeep et al.[21] found that almost a third of patients with nonalcoholic chronic pancreatitis were with low bone density while it was detected only in 9% of the healthy comparators. Dugan SN et al[4]also found that a third of CP patients were with osteoporosis. Recently published systematic review with a meta-analysis [5] showed that one out of four patients with chronic pancreatitis had osteoporosis and two-thirds had either osteoporosis orosteopenia. The most important consequence of that is higher risk of low-trauma fractures. Interestingly, CP patients are at a higher risk of low-trauma fractures than patients with Crohn's disease[22].

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 fearing

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steatorrhea-related symptoms. Other important contributing factor is chronic inflammation, related protein-energy malnutrition[11] and consequent bone mineral loss. Similarly to the patients with inflammatory bowel disease, certain inflammatory mediators IL-1, IL-6, TNF-α and IFN-g. contribute to bone loss [23].

Conclusion

In patients with chronic pancreatitis and severe structural changes prevails low vitamin D levels regardless of the season of sampling. PEI and diabetes presence could 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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Disclosure statement

No potential conflict of interest was reported by the authors.

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