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Review Article

Systematic review and meta-analysis on the prevalence of vitamin D deficiency in patients with chronic pancreatitis

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ABSTRACT

Background/objectives: Patients with chronic pancreatitis (CP) are at risk of malnutrition due to malabsorption, pain and/or alcohol consumption. This can cause vitamin D insufficiency or deficiency, which is associated with osteoporosis and increased risks of fractures. We aimed to perform a meta-analysis to determine the prevalence of vitamin D insufficiency and deficiency in CP patients. Furthermore, we compared these results with healthy controls.

Methods: We performed a systematic review and meta-analysis on the literature by searching PubMed and EMBASE (January 2000–December 2015) on CP and vitamin D. Primary outcome was prevalence of vitamin D insufficiency (<75 nmoL/L) and deficiency (<50 nmoL/L) in CP patients. When available, data of CP patients were compared with healthy controls.

Results: Nine studies were included in our meta-analysis, reporting on the prevalence of vitamin D insufficiency/deficiency in 465 patients (mean age 41 years (range 18–60), 81% male) and in 378 controls (mean age 40 years (range 18–67), 76% male). Pooled prevalence of vitamin D insufficiency and deficiency in CP patients was 83% and 65%, respectively. Calculated odds ratio (OR) of vitamin D insufficiency and deficiency between CP patients and controls was 1.34 (0.54–3.29) and 1.14 (0.70–1.85), respectively ($p > 0.05$).

Conclusion: There is a high prevalence of vitamin D insufficiency and deficiency in CP patients. Nevertheless, there is no significant difference in prevalence of vitamin D insufficiency and deficiency compared to healthy controls. Further research should indicate the clinical relevance and consequences of these findings for clinical practice.

1. Introduction

Chronic pancreatitis (CP) is an inflammatory disease, characterized by fibrosis of the pancreas and loss of acinar and islet cells, which can lead to endocrine and exocrine insufficiency [1]. Patients suffering from CP are at risk of malnutrition, because of poor diet due to pain and/or excessive use of alcohol. There is also an increased risk of malabsorption, caused by exocrine pancreatic insufficiency (EPI) [2–4]. EPI can imply impaired fat absorption, which can lead to deficiency of fat soluble vitamins A, D, E and K, especially in patients with malnutrition. Low levels of vitamin D are associated with decreased absorption of calcium from the gut [5], which causes increased levels of parathyroid hormone (PTH) [6,7]. Increased PTH subsequently stimulates calcium resorption from bones. In the long term, this can lead to osteoporosis, which causes an increased risk of bone fractures [8]. Low vitamin D serum levels also increase the risk of muscle weakness [9], colorectal cancer [10], cardiovascular disease [11] and depression [12]. Early detection and treatment of vitamin D deficiency in CP patients might prevent development of these complications.

Because of these known consequences of vitamin D deficiency it has been recommended to regularly determine all fat-soluble vitamin serum levels and to give vitamin D supplementation in all patients with CP [1,4]. However, a systematic review and meta-analysis on the prevalence of vitamin D insufficiency and deficiency in CP patients to support these recommendations has not yet been performed. Therefore, the aim of this systematic review was to

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evaluate the prevalence of vitamin D insufficiency and deficiency in patients with CP and to compare these results with healthy controls.

2. Methods

2.1. Study selection

A literature search was performed in PubMed and EMBASE between January 2000 and December 2015 on the.terms *chronic pancreatitis* and *vitamin D* in title and/or abstract.

All identified publications were screened on title and abstract by two reviewers (SH and SL). Possible relevant full text articles were also reviewed by two reviewers (SH and SL). Inclusion criteria were: publications reporting on CP patients with prevalence of vitamin D deficiency and/or insufficiency for 1,25$(OH)_2$ vitamin D or 25(OH) vitamin D. Exclusion criteria were: studies not written in English, reviews, studies with preselected vitamin D deficient patients, patients with liver/cholestatic disease, inflammatory bowel disease, cystic fibrosis or other comorbidity that could affect vitamin D metabolism.

2.2. Quality assessment

Quality of included articles was scored using the Newcastle – Ottowa Scale for observational studies [13]. This scale uses a star system to score quality of studies on three items: selection and comparability of the study groups and the ascertainment of exposure. Studies can obtain a maximum of 9 stars. Quality of the selection procedure of study groups is estimated based on adequate definitions of cases and controls, representativeness of the cases for patients with CP and if controls and cases are from the same comparable community. Definition of CP was regarded correct if studies mentioned using a validated checklist for diagnosis (e.g. M-ANNHEIM diagnostic criteria [14], Japan Pancreas Society diagnostic criteria [15]) or when diagnosis was well defined, based on typical clinical and imaging features. Every study can obtain a maximum of 4 stars for quality of the selection procedure. Two stars can be given for comparability, if controls and cases are matched for one (1 star) or more (2 stars) characteristics. At last, 3 stars can be obtained if the ascertainment of CP or no CP is defined and if the percentages of deficits/lost to follow up are the same in both groups. We determined that studies with 7 stars or more were assumed to be of high quality, and less than 7 stars to be of lower quality.

2.3. Data extraction

Data on study design, publication year, country of origin, number of subjects, age, gender, etiology of CP, Cambridge classification, presence of EPI, treatment with pancreatic enzyme replacement therapy (PERT), vitamin D serum levels, Parathyroid hormone (PTH) serum levels, T-scores and prevalence of vitamin D deficiency and insufficiency were, if noted, extracted. All studies that compared CP patients and healthy controls were also pooled to evaluate differences in prevalence of vitamin D deficiency and insufficiency between these groups.

2.4. Outcome measures

There is no unequivocal definition for 25-hydroxy-vitamin D (25-OH-D) deficiency/insufficiency. We defined deficiency as vitamin D < 50 nmoL/l or 1,25 (OH)2 D < 38 pmoL/l and insufficiency as vitamin D between 50 and 75 nmoL/l [16,17]. The reference range of PTH serum level is between 0.6 and 6.7 pmoL/L. Bone mineral density was expressed in T-scores and these were calculated using a central dual-energy x-ray absorptiometry. T-score values between +1.0 and −1.0 were considered normal. Severity of CP was determined using the Cambridge classification [18]. This system classifies CP into mild, moderate or severe CP based on structural changes of the pancreas and abnormalities of the PD and/or its side branches. Patients were considered to have EPI based on pancreatic function tests, namely fecal elastase test or 72-h fecal fat test. Exocrine pancreatic function was considered insufficient when fecal elastase level was <200 μg/g feces or when fecal fat was ≥18 g fat/72 h.

2.5. Statistical analysis

Descriptive statistics were computed for all study variables. Categorical data were reported as frequency and percentage. Continuous data were reported as mean ± standard deviation (SD) or as median (range), depending on the distribution.

Primary outcome of interest was the pooled prevalence of vitamin D insufficiency and deficiency in patients with CP. A meta-analysis was performed to determine the prevalence of vitamin D insufficiency and deficiency in patients with CP, following the technical note of Nyeloff et al. [19]. The 95% confidence interval (CI) of each study was determined using the formula of Wilson [20]. A random effects model was used for the calculation of the pooled prevalence and 95% CI. This model does not assume that differences between studies derive from hazard. It approximates a mean prevalence of the included studies by representing all effect sizes, in order to not be predominantly influenced by one large study [21]. I^2-test of Higgins et al. [22] was used to estimate the heterogeneity in percentages between studies that cannot be explained by chance. The closer this value is to zero, the less variability there is between studies. Negative values are comparable with zero and mean no heterogeneity. Values below 25% suggest low, between 25% and 50% moderate and above 50% high heterogeneity between studies.

The odds ratio (OR) for prevalence rates of vitamin D insufficiency and deficiency between CP patients and controls were compared for all studies that included a healthy control group. The OR was calculated using a random effects model. Mean difference of vitamin D mean serum levels between CP patients and controls were calculated as well. P values < 0.05 were considered statistically significant. Microsoft Excel 2010 was used for calculation of the pooled prevalence of vitamin D insufficiency and deficiency. Review Manager (v.5.3.5) was used for analysis of the OR and the mean difference.

3. Results

3.1. Search results and study characteristics

The selection process is shown in Fig. 1. Manual searches of the references of the included articles did not provide additional articles. In total, nine studies were included reporting on vitamin D deficiency/insufficiency with 465 CP patients and 378 controls [4,17,23–29] (Table 1). Prevalence of vitamin D insufficiency was reported in six studies [4,24,26–29] and prevalence of vitamin D deficiency was reported in seven studies [4,17,23,25,27–29] (Table 2).

3.2. Patient characteristics

Altogether, 317 (68.2%) men and 111 (23.9%) women were included, the gender of 37 (7.9%) patients was unknown [26]. Two studies only included men [24,25], six studies included both men and women [4,17,23,27–29] and one study did not mention gender

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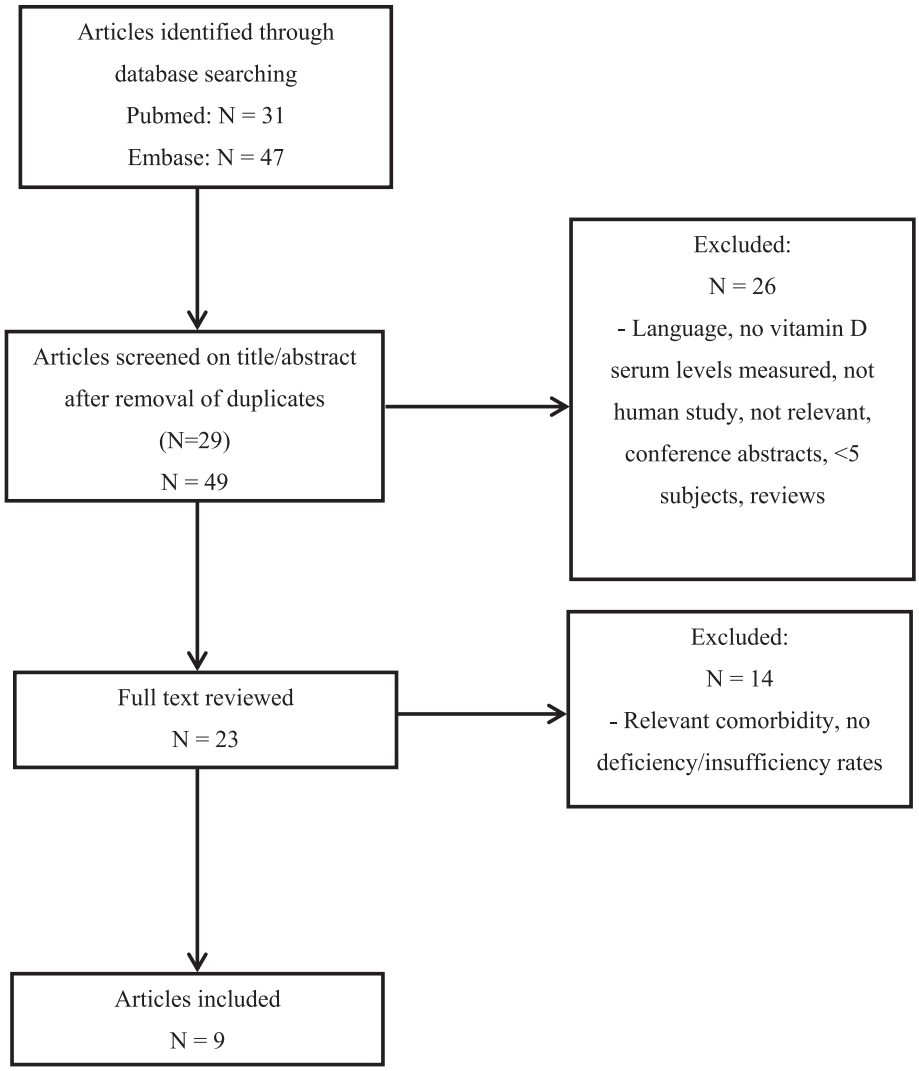

Fig. 1. Selection of studies reporting on vitamin D deficiency/insufficiency in patients with CP.

Table 1
Included studies and patient characteristics.

Author, year (study design)	Subjects				Age, years in mean (±SD)		Etiology CP No.(%)			EPI (%)	PERT (%)
	CP patients (CP)	Controls (C)	Male CP (%)	Male C (%)	CP	C	Alcoholic	Tropical	Idiopathic		
Pezzilli et al., 2015 (Case - study)	30	–	15 (50)	–	57.0 (13.1)	–	–	–	–	17 (57)	NS
Duggan et al., 2015 (Case - control)	29	29	17 (59)	17 (59)	44.3 (12.3)	45.8 (9.8)	18 (62)	–	11 (28)	NS	NS
Prabhakaran et al., 2014 (Case - control)	91	40	91 (100)	40 (100)	38.6 (20.6)	36.7 (20.7)	64 (70)	–	26 (29)	NS	NS
Sikkens et al., 2013 (Cohort)	40	–	23 (58)	–	52 (11)	–	20 (50)	–	17 (43)	28 (70)	19 (48)
Duggan et al., 2012/2014 (Case - control)	62	66	45 (73)	48 (73)	47.9 (12.5)	47.7 (11)	24 (39)	–	–	16 (35)[a]	NS
Klapdor et al., 2012 (Case - control)	37	108	–	–	–	–	–	–	–	37 (100)	37 (100)
Sudeep et al., 2011 (Case - control)	31	35	31 (100)	35 (100)	35.8 (9.0)	38.6 (5.2)	–	20 (65)	11 (35)	21 (68)	0 (0)
Joshi et al., 2011 (Case - control)	72	100	38 (53)	50 (50)	31.1 (10.3)[b]	32.6 (9.6)	–	72 (100)	–	41 (88)[c]	33 (46)
Dujsikova et al., 2008 (Case - study)	73	–	57 (77)	–	46.6 (13.2)	–	–	8 (11)	65 (89)	NS	NS

*CP = chronic pancreatitis, SD = standard deviation, NS = not specified, EPI = exocrine pancreatic insufficiency, PERT = pancreatic enzyme replacement therapy.
[a] Tested only 46 patients on EPI.
[b] Included 4 minors (13–18 years).
[c] Tested only 43 patients on EPI.

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Table 2
Serum levels of vitamin D and PTH, prevalence of vitamin D insufficiency/deficiency and T-scores in original studies.

Author, year	Vitamin D in nmol/l			Vitamin D insufficiency in %			Vitamin D deficiency in %			PTH in pg/ml			T-scores femoral neck		
	CP	Controls	p	CP	Controls	p	CP	Controls	p	CP	Controls	p	CP	Controls	p
Pezzilli et al., 2015	30.5 (21.0)	–	–	86.7	–	–	80.0	–	–	13.5 (2.0)	–	–	–	–	
Duggan et al., 2015	31.0 (39.5)	42.0 (32.5)	<0.05	–	–	–	68.2	62.1	0.4	47.1 (19.4)	46.3 (14.0)	NS	[f]	[f]	<0.05
Prabhakaran et al., 2014	67.4 (130)	94.8 (65)	<0.05	68.1	–	–	–	–	–	27.6 (39.8)	27.5 (34.2)	NS	−1.7 (−2.7)	–	–
Duggan et al., 2014/2012	47.5 (21.6)	46.4 (20.4)	NS	93.5	28.3	0.9	58.1	61.7	0.9	–	–	–	−0.8	−0.1	<0.05
Sikkens et al., 2013	40.0 (23–85)[d]	–	–	–	–	–	52.5	–	–	–	–	–	−0.9 (−1.7 – −0.2)[e]	–	–
Klapdor et al., 2012	37.4 (32.4)	43.7 (24.2)	N/A	86.5	87	–	–	–	–	–	–	–	–	–	–
Sudeep et al., 2011	37.4 (12.5–130)[e]	55.4 (14)	<0.05	–	–	–	51.6	24	<0.05	–	–	–	–	–	–
Joshi et al., 2011	24.0 (17.3–42.0)[e]	27.5 (20.5–37.5)[e]	0.88	94.4	96.0	0.2	86.1	85	0.2	43,4 (13.2–308.1)[e]	84.9 (55.7–132.1)[e]	<0.05	[f]	[f]	<0.05
Dujsikova et al., 2008	–	–	–	86.3		–	54.8	–	–	–	–	–	–	–	–

*Data reported as mean (± standard deviation), CP = chronic pancreatitis, PTH = parathyroid hormone, p = p-value, NS = not significant, N/A = not applicable.
[d] Median (range) and 1,25$(OH)_2$ D value. Reference range: deficiency <38 pmoL/L.
[e] Median (range).
[f] T-scores were significantly lower at all areas in CP patients (L1-L4, right femoral neck, total hip).

[26]. Mean age was 41 years (range 18–60 years). CP was classified as alcoholic in 126 (27.1%) patients, idiopathic in 130 (28.0%), tropical calcifying pancreatitis in 100 (21.5%), post-traumatic in one (0.2%) other (auto-immune, hereditary) in 3 (0.7%) and aetiology was not specified in 105 (22.5%) patients. In 238 (51.2%) patients Cambridge classification was determined; 78 (32.6%) patients had mild, 39 (16.5%) had moderate and 121 (50.9%) had severe CP. Six studies tested exocrine pancreatic function: Five studies [4,17,26,27,29] applied a fecal elastase test and one study [25] a 72-h fecal fat test, From the 197 (42.4%) patients in whom a pancreatic function test was performed, 140 (71.1%) had EPI (Table 2).

3.3. Control characteristics

Six studies included a control group (4, 23–27). Controls were matched in 5 out of 6 studies with CP.

patients. In total, 378 healthy subjects were included: 190 (50.3%) men, 80 (21.2%) women and 108 (28.5%) unknown gender [26]. (Table 2). Mean age of controls was 40 years (range 18–67 years).

3.4. Quality assessment included studies

Included articles were critically appraised. Five studies [23–25,27,30] obtained 7 stars or more and can be seen as high quality studies. Two studies of Duggan et al. [4,31] were merged, because they used the same study group and design. Four studies [17,26,28,29], gained 4 stars or less and can be seen as lower quality studies. Three of them were case studies without control group and therefore obtained 3 stars. The last study [26] was a case-control study about EPI patients which included a small subgroup of CP patients. It was not mentioned how CP was diagnosed, nor how the control group was selected and they did not match case characteristics with control group. Therefore they obtained only four stars.

3.5. Vitamin D insufficiency and deficiency in patients with chronic pancreatitis

The pooled prevalence of vitamin D insufficiency in CP patients was 83.2% (95% CI: 74.0%–92.4%). Computed I^2 was 1.5% (Fig. 2).

The pooled prevalence of vitamin D deficiency was 65.4% (95% CI

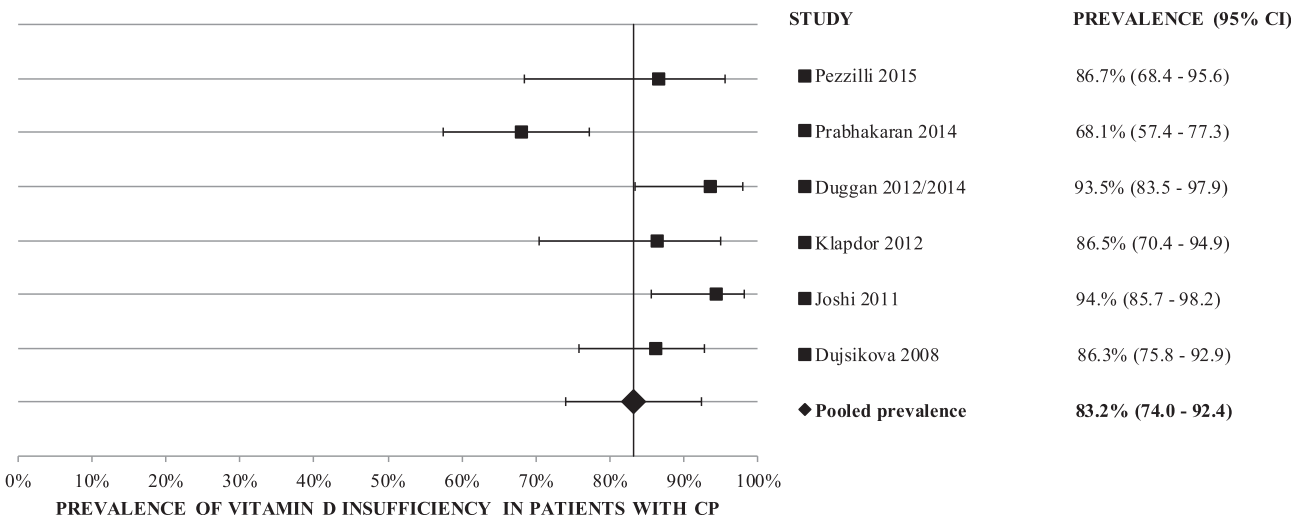

Fig. 2. Pooled prevalence of vitamin D insufficiency in patients with CP.

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55.2%–75.5%). Calculated I^2 was −4.0% (Fig. 3).

3.6. Vitamin D insufficiency and deficiency in CP patients versus controls

Three studies (171 CP patients and 274 controls) were included in the calculation of the OR of vitamin D insufficiency in CP patients versus controls [4,26,27]. Calculated OR was 1.34 (0.54–3.29), which was not significant ($p = 0.20$). I^2 was 38% (Fig. 4).

For calculation of the OR of vitamin D deficiency in CP patients versus controls three studies were included (163 CP patients and 195 controls) [4,23,27]. Calculated OR (1.14 (0.70–1.85)) was not significant ($p = 0.60$) and computed I^2 was 0% (Fig. 5).

3.7. Vitamin D serum levels in CP patients versus controls

Three studies were applicable for calculation of the mean difference of the mean serum levels in CP patients (182) versus controls (135) [4,23,24]. Remaining studies reported median serum levels of vitamin D or did not include a control group (Table 2). Calculated mean difference was −6.38 (−20.07–7.32), suggesting that the mean vitamin D serum level in CP patients is approximately 6.38 nmoL/L lower than in controls. However, this difference was not significant ($p = 0.36$) and calculated I^2 was 48%.

4. Discussion

The prevalence of vitamin D insufficiency and deficiency in patients with CP is high. However, there was no significant difference in vitamin D insufficiency and deficiency between CP patients and healthy controls. In fact, even though the number of studies included is limited, prevalence of vitamin D insufficiency and deficiency seems to be high in healthy controls as well.

There are several factors that might influence prevalence of

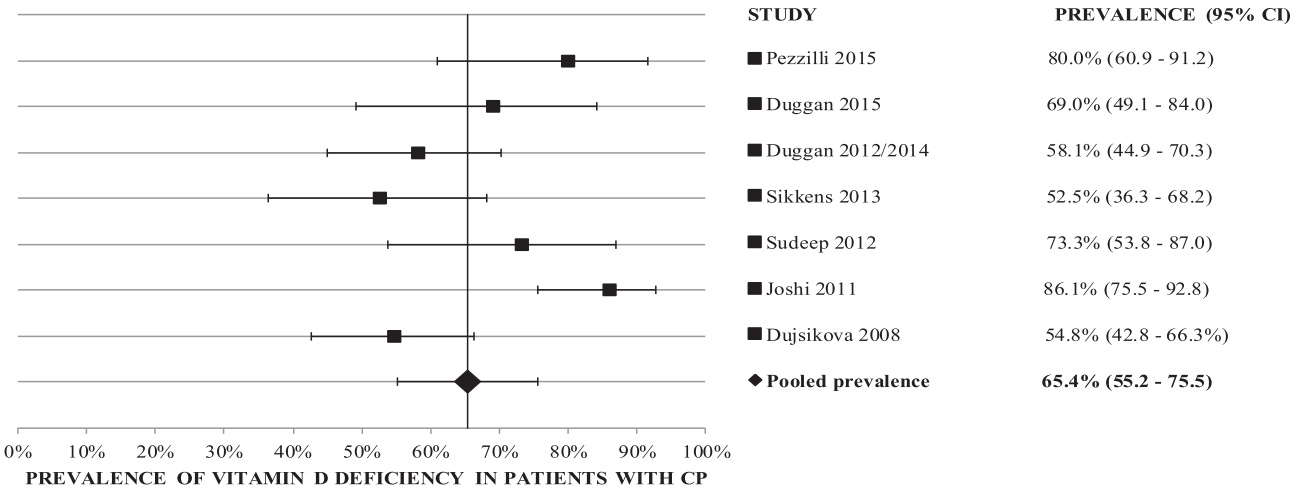

Fig. 3. Prevalence of vitamin D deficiency in patients with CP.

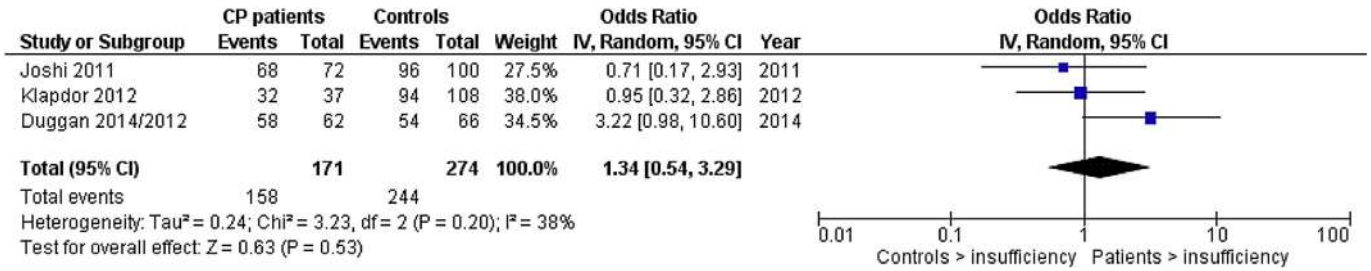

Fig. 4. Odds ratio vitamin D insufficiency between CP patients and controls.

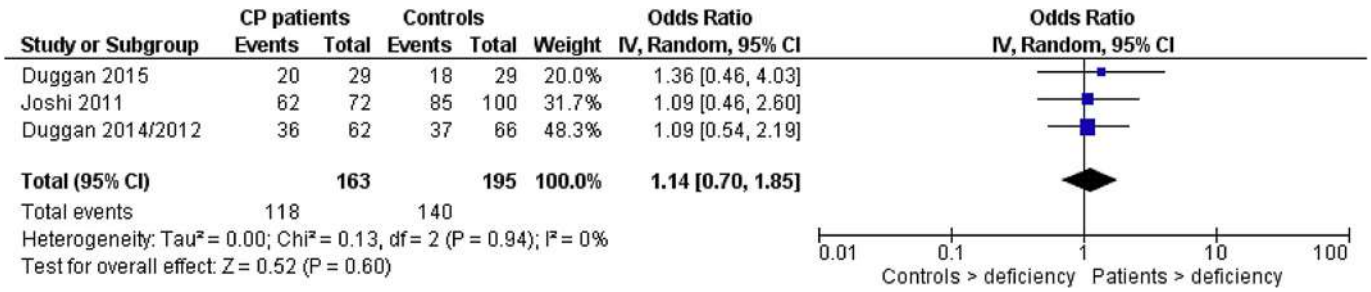

Fig. 5. Odds ratio vitamin D deficiency between CP patients and controls.

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decreased vitamin D in patients with CP. Only four studies reported on the influence of EPI on the risk of vitamin D deficiency [4,6,17,29]. Sikkens et al. [17] and Mann et al. [6] showed that the prevalence of vitamin D deficiency was higher in CP patient with EPI compared to CP patients without EPI. However, Duggan et al. [4] and Pezzelli et al. [29] did not find a correlation of fecal elastase-1 and vitamin D. Other studies did not look at differences in patients with or without EPI. In general, patients with EPI are treated with PERT. A recent study reported that vitamin D levels of CP patients with EPI are increased when they are treated with PERT compared to CP patients with EPI who are not treated with PERT [17]. Nevertheless, they also showed that vitamin D levels in patients who use PERT are still decreased compared to CP patients without EPI, suggesting that this therapy alone might not be sufficient [17,32]. Other complications of CP that influence nutrition are chronic abdominal pain, diabetes mellitus, continuing alcohol consumption, avoidance of fat-rich meals due to fear of steatorrhea and persistence of steatorrhea after PERT, causing continuous risk of malnutrition [17, 33].

Malnutrition and malabsorption are probably not the only factors accountable for vitamin D insufficiency and deficiency in CP patients. Vitamin D is also synthesized in the skin under the influence of sun exposure. This vitamin D synthesis might be responsible for 80–90% of the circulating vitamin D [34]. Seasonal differences and latitude differences in vitamin D serum levels are shown in several studies [35–37]. Besides, chronic illness can also negatively influence exposure to sunlight and thus vitamin D synthesis. Therefore, it is important to point out lack of sunlight exposure as indication for vitamin D deficiency in patients with CP.

One of the main complications of vitamin D deficiency is decreased bone mineral density (BMD), which can lead to osteoporosis and bone fractures. A recent systematic review showed a high prevalence of osteoporosis in patients with CP [30]. However, they did not compare the prevalence of osteoporosis with healthy controls. A large retrospective cohort study on the low-trauma fracture risk in GI-diseases reported a significant higher risk of low trauma fractures in patients with CP (3192 subjects) compared with controls (1436699 subjects) (4.8% vs 1.1%) [38]. Although these findings indicate that known complications of vitamin D deficiency occur often in CP patients, Duggan et al. [31] could not find a direct association between low vitamin D and reduced BMD in CP patients. Therefore, it is unclear if decreased values of vitamin D are the decisive cause for the high prevalence of osteoporosis and low trauma fractures in patients with CP.

Although several studies reported a significant difference in mean vitamin D levels between CP patients.

and controls [24–26,39,40], we did not find a significant mean difference in vitamin D levels in our meta-analysis. Duggan et al. (2015) [23] reported that prevalence of vitamin D deficiency was significant higher in CP patients than in controls when using a lower cut-off value (30 nmoL/L) for vitamin D deficiency. Since decreased BMD, caused by low vitamin D serum levels, are only reported when serum levels <25 nmoL/L, the definition of vitamin D deficiency might be reconsidered [41]. Still, PTH serum levels are starting to rise if vitamin D < 78 nmoL/L and increased PTH serum levels can eventually lead to a decrease in BMD [35,42,43].

Vitamin D insufficiency might be a more generalized health problem that extends to the complete population, not specifically in patients with CP. A recent large cohort study in 470 healthy European-Americans (35% men, mean age 39.5 (19–86)) and 179 native Americans (26% men, mean age 41.9 years (19–74)) confirmed this and reported vitamin D deficiency in respectively 51.9% and 66.5% of their healthy population [44]. We found that the prevalence of vitamin D deficiency is 65.4%, which seems to be comparable, at least with the native Americans. Another large cohort study (n = 1569) in a healthy population in France reported low mean serum levels of vitamin D (61 nmoL/L ± 30) [35], which seems higher than most serum levels of CP patients reported in the included studies (Table 2).

This study has several limitations. Nine studies reported on vitamin D deficiency or insufficiency in CP patients, of which five were considered as high quality. Since only three of them reported on the prevalence of deficiency and/or insufficiency of vitamin D in healthy controls, the number of patients in this meta-analysis is limited. Sikkens et al. [17] divided CP patients in groups who were exocrine pancreatic sufficient, insufficient or insufficient but treated with PERT. The other included studies mentioned only that some people were treated for EPI, but not if those patients differed in outcomes considering vitamin D deficiency in comparison to the untreated group. Therefore a possible influence of EPI and PERT on prevalence of vitamin D insufficiency and deficiency could not be evaluated. In addition, some studies included patients who were taking vitamin supplements, what may also influences the prevalence of vitamin D insufficiency and deficiency. These limitations should be taken in consideration while reading this review. A large case-control study is necessary to determine mean vitamin D levels, PTH, bone mineral density, disease severity/EPI and the prevalence of vitamin D insufficiency/deficiency in patients with CP and matched, healthy controls. Follow up of vitamin D serum levels and BMD in CP patients versus controls might determine if there is an association and increased risk of low vitamin D and decreased BMD in patients with CP. The need for vitamin D supplementation in (a subset of) patients with CP should be evaluated, as well the effect of supplementation on clinical outcome.

In conclusion, CP patients are at high risk of vitamin D insufficiency and deficiency. Influence of disease severity, EPI or PERT use on prevalence of deceased vitamin D is unclear. Since the prevalence of vitamin D deficiency seems to be high in the healthy population as well, it is uncertain what the clinical consequences of these findings are. Based on current knowledge, recommendations to regularly determine fat soluble vitamin serum levels in patients with CP is not evidence-based. More research is needed to determine the prevalence of vitamin D deficiency in CP patients in comparison with the general population and to evaluate the (long-term) clinical consequences of this problem.

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