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ORIGINAL ARTICLE

High-Dose Vitamin D and Early Chronic Pancreatitis-Related Changes After Acute Pancreatitis: A Randomized Dose Controlled Trial

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Abstract

Objectives Chronic pancreatitis (CP) is an irreversible condition with multiple comorbidities. Pancreatic stellate cells (PCSs) are crucial in the fibrotic process in CP. PSCs have a regulating vitamin D receptor. The aim was to assess if a daily higher dose of vitamin D can prevent the progression to CP in patients after the first episode of acute pancreatitis (AP).

Methods This was a single-centre randomized placebo -controlled trial. Patients were randomized after the first episode of AP to either a daily 100 µg high-dose vitamin D (HDVD) or a 10 µg low-dose vitamin D (LDVD) groups. Follow-up included magnetic resonance imaging (MRI), laboratory tests and QoL questionnaires (QLQ-C30 and Pan26). The development of parenchymal changes possibly related to fibrosis after AP in MRI.

Results Sixty-nine patients were recruited. There was a high dropout (51%), therefore the final analysis included all patients who completed the three or two years of trial: in total 34 patients. No definitive CP cases occurred in HDVD group, while one was observed in LDVD group ($p=0.367$). Less CP related findings developed during the trial in the HDVD compared to the LDVD group ($n=4$ vs $n=13$, $p=0.016$). The HDVD patients had a significantly lower pain score than the LDVD group ($p=0.019$). Vitamin D levels were significantly higher in HDVD group compared to LDVD group without adverse effects.

Conclusions HDVD after AP was linked to fewer early CP-related changes during 2–3 years of follow-up. These preliminary findings warrant confirmation in larger trials with longer observation**.** Long-term interventional trials are challenging in this patient group.

Trial registration number: ClinicalTrials.gov: NCT02965898.

Keywords Acute pancreatitis · Chronic pancreatitis · Prevention · Fibrosis · Pancreatic stellate cell · Cholecalciferol · Vitamin D3

Introduction

Chronic pancreatitis (CP) is characterized by fibrosis of pancreatic tissue and morphological changes in the parenchyma, such as pancreatic duct dilation and calcification. These changes may lead to complications such as bile duct obstruction and pseudocysts [1, 2]. The disease may progress to pancreatic insufficiency and persistent or recurrent abdominal pain, which not only significantly lowers patients' quality of life but also necessitates invasive interventions and is associated with a reduced life expectancy [3–6].

The fibrotic process in the pancreatic parenchyma is regulated by pancreatic stellate cells (PSCs), which play a key role in stromal interactions that control the production of the pancreatic extracellular matrix. Therefore, PSCs are considered to be central mediators of fibrosis in both CP and pancreatic cancer. In their dormant state, PSCs are largely inactive; however, they can be activated through various pathways, including exposure to alcohol, cell injury, cigarette smoking, hyperglycemia, or even pressure from the pancreatic duct. Inflammatory cells, particularly

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macrophages, and pancreatic acinar cells also play a role in activating PSCs. Certain genetic mutations, such as SPINK1, have been linked to PSC activation through macrophages [7, 8].

PSCs have been found to express a vitamin D receptor, which regulates both inflammation and fibrosis. In murine models, vitamin D3 (calcitriol), a form of vitamin D, has been shown to downregulate fibrosis associated with CP [9, 10].

The aim of this study was to investigate whether the highest recommended daily dose of vitamin D can prevent CP-related parenchymal changes related to fibrosis in the pancreas following acute pancreatitis (AP). As a secondary outcome, we also sought to determine if higher doses of vitamin D could reduce development of CP, the incidence of recurrent acute pancreatitis (RAP) and improve quality of life (QoL).

Methods

Study Design

This study was a single-center, prospective, randomized, dose-controlled trial conducted at Tampere University Hospital. The study was introduced to patients who were treated for their first episode of AP. After providing written informed consent, patients were randomized into one of two groups: the high-dose vitamin D (HDVD) group, which received a daily dose of 100 µg of Vitamin D3 (cholecalciferol), or the low-dose vitamin D (LDVD) group, which received 10 µg of Vitamin D3 daily, in accordance with national health recommendations. The packaging of the vitamin doses were blinded by code, and only the research nurses knew the dosages until analysis.

Exclusion Criteria

Patients were excluded if they had a previous history of pancreatitis, a diagnosis of CP, chronic kidney insufficiency (estimated glomerular filtration rate < 60), hypercalcemia, or toxic vitamin D levels (25-hydroxyvitamin D levels > 375 nmol/L).

Randomization

Randomization was performed between November 2016 and January 2022 by research assistants using block randomization, with blocks of four, ensuring that each block contained an equal number of participants in both the high-dose vitamin D (HDVD) and LDVD groups (two participants in each group) [13]. Neither the patients, researchers, nor the treating physicians knew the assigned dose until the analysis of the results began. The randomization code was maintained by the research assistant. The vitamin D supplement used was DeviSol® (Orion Pharma, Espoo, Finland).

Follow-up and Assessments

Following their first episode of AP, study participants had follow-up visits at 1 to 3 months and annual follow-ups at 2- to 3-year intervals. Follow-up assessments included annual laboratory tests (blood and stool samples), upper abdominal magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP), and quality of life (QoL) questionnaires (EORTC QLQ-C30 and PAN26). The Alcohol Use Disorders Identification Test (AUDIT) was also completed.

The fibrotic replacement of pancreatic parenchyma was estimated in axial MR-images by measuring the parenchymal thickness in using T2-weighted sequence and using T1-weighted sequences without fat saturation in detecting parenchymal signal intensity changes. In addition, the pancreatic duct morphology was estimated from MRCP-images and parenchymal calcifications from abdominal computed tomography (CT) scans when available.

A final follow-up was conducted 5–8 years after the start of the trial to assess any possible readmissions because of RAP or CP.

The MRI images were analyzed blind by an experienced abdominal radiologist who was blinded to the randomization group. Laboratory tests included a complete blood count, albumin, amylase, fasting glucose, glycated hemoglobin (HbA1c), 25-hydroxyvitamin D (vitamin D-25), ionized calcium, blood creatinine, and fecal elastase-1 (FE1).

Classification of AP and CP

A was classified according to the revised Atlanta criteria [14]. CP was classified according to the M-ANNHEIM diagnostic criteria as either definitive or probable [15].

- **Definitive CP** was diagnosed if one or more of the following criteria were met: enlarged pancreatic main duct, pancreatic calcifications, pancreatic exocrine insufficiency (PEI) with steatorrhea that improved with pancreatic enzyme replacement therapy, or typical histological findings (not applicable in this study).
- **Probable CP** was diagnosed if one or more of the following criteria were met: mild ductal changes, recurrent or persistent pseudocysts, laboratory indicators of endocrine insufficiency (abnormal fasting glucose or high HbA1c), or PEI (as indicated by low FE1) were present.

Endocrine insufficiency was defined as diabetes mellitus with a fasting glucose > 7.0 mmol/L or an HbA1c > 48 mmol/mol [16]. PEI was indicated by an FE1 level < 200 µg/g [17].

Outcomes

The primary outcome was the presence of CP-related parenchymal findings (pancreatic atrophy and fibrosis).

Secondary outcomes included the development of CP according to the M-ANNHEIM criteria (including ductal changes, pancreatic calcification, low FE1 levels, persistent pseudocysts, new-onset diabetes), RAP and quality of life (QoL).

Statistical Analysis

The hypothesis of this study was that 30% of patients would exhibit parenchymal changes in their MRI after three years, and that administering a high dose of vitamin D following the first episode of AP could reduce CP-related parenchymal changes to 15%. Based on this assumption, along with an expected dropout rate of 15%, a power of 80%, and an α-level of 0.05, the required sample size was calculated to be 130 patients. However, due to recruitment challenges and participant dropout, the final sample size was smaller than anticipated. A total of 69 patients were recruited and the final analysis included 34 patients who completed two or three years of follow-up.

Laboratory and AUDIT scores are presented as medians with interquartile range (IQR) in parentheses (Tables 1 and Table 2). Data are reported as medians (range), and EORTC QLQ-C30 response scores are presented as means with standard deviation (SD), unless otherwise specified.

Pearson's chi-square test was used for categorical variables. Linear regression was used to analyze normally distributed continuous variables (e.g., EORTC QLQ-C30 Global Health Status and QoL), while the Mann–Whitney U test was applied to non-normally distributed variables (the remaining EORTC QLQ-C30 parameters). Any possible missing data was left out of the analysis. Analysis was performed on a per protocol analysis basis.

All statistical analyses were performed using IBM SPSS® (Armonk, NY) version 28. A p-value of < 0.05 was considered statistically significant.

Ethics

The study was approved by the Ethics Committee of Tampere University Hospital, Finland (Ethical Committee code R16004). It was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki [18]. Informed written consent was obtained from all participants. The study was registered in ClinicalTrials.gov (ID: NCT02965898).

Participants were assigned to receive either the nationally recommended dose of 10 µg or a higher dose of 100 µg of Vitamin D3. The European Food Safety Authority

Table 1 Baseline characteristics of patients after their first acute pancreatitis episode, grouped by high-dose vitamin D (HDVD) and low-dose vitamin D (LDVD) groups

Baseline characteristics	High-dose vitamin D group $n = 15$	Low-dose vitamin D group $n = 19$	p-value
Age (years) median (IQR)	54 (46–64)	55 (49–62)	0.89
Gender (male/female)	86%/14%	68%/32%	0.21
Severity of first AP			
Mild	71%	95%	0.08
Moderately severe	29%	5%	0.08
Severe	0%	0%	
Etiology of first AP			
Alcohol	11 (73%)	11 (58%)	0.35
Biliary	1 (7%)	3 (16%)	0.41
Idiopathic	3 (20%)	5 (26%)	0.67
Hypertriglyceridemia	0 (0%)	1 (5%)	0.37
Smoking	3 (21%)	7 (37%)	0.24
AUDIT score median (IQR)	10 (6–17)	7 (3–16)	0.72
Laboratory tests median (IQR)			
Vitamin-D-25 (nmol/l)	69 (52–80)	60 (52–86)	0.81
Ionised Calcium (mmol/l)	1.26 (1.22–1.28)	1.24 (1.23–1.28)	0.98
Fecal Elastase-1 (µg/g)	482 (308–500)	429 (308–500)	0.44
Fasting glucose (mmol/l)	6.3 (5.7–6.9)	6.2 (5.7–6.6)	0.58
HbA1c (mmol/mol)	38 (34–43)	38 (36–43)	0.79

Table 2 Results after 2–3 years of treatment with either 100 µg (HDVD) or 10 µg (LDVD) of daily vitamin D

Final outcome	High-dose vitamin D group $n=15$	Low-dose vitamin D group $n=19$	p-value
Pancreatic fibrosis	1 (7%)	4 (21%)	0.24
Any signs of CP (possible or definitive criteria)	4 (27%)	13 (68%)	**0.016**
Possible chronic pancreatitis	4 (27%)	12 (63%)	**0.034**
Definitive chronic pancreatitis	0 (0%)	1 (5%)	0.367
Recurrent pancreatitis	3 (20%)	5 (26%)	0.67
AUDIT score *median (IQR)*	4 (2–12)	2 (0–4)	0.13
Imaging findings			
Normal pancreas	8 (53%)	6 (32%)	0.2
Atrophy	0 (0%)	2 (11%)	0.63
Pancreatic IPMN	3 (20%)	2 (11%)	0.8
Pancreatic pseudocyst	4 (27%)	6 (32%	0.78
Sideduct dilation	1 (7%)	4 (21%)	0.24
Main duct dilation	1 (7%)	0 (0%)	0.25
Parenchymal calcification	0 (0%)	1 (5%)	0.37
Laboratory tests			
Vitamin-D-25 (nmol/l) *median (IQR)*	131 (107–142)	58 (54–69)	**< 0.001**
Ionised Calcium (mmol/l) *median (IQR)*	1.24 (122–1.27)	1.23 (1.21–126)	0.34
Fecal Elastase-1 (ug/g) *median (IQR)*	500 (330–670)	500 (320–500)	0.54
Fecal Elastase-1 under 200 (ug/g)	0 (0%)	4 (21%)	0.06
Fasting glucose (mmol/l) *median (IQR)*	6.10 (5.6–6.6)	5.7 (5.4–6.8)	0.70
HbA1c (mmol/mol) *median (IQR)*	40 (36–44)	40 (38–44)	0.37
HbA1c > 48 mmol/mol	0 (0%)	4 (21%)	0.06
Amylase > 120 U/l	0 (0%)	1 (5%)	0.37

IQR interquartile range, *CP* chronic pancreatitis, *AUDIT* alcohol use disorders identification test, *HbA1c* glycated haemoglobin, *IPMN* intraductal papillary mucinous neoplasm

p-values marked with bold indicate statistically significant differences between the groups

recommends a maximum safe daily dose of 100 µg of Vitamin D3, and daily doses up to 250 µg have been shown to be safe without adverse effects [19].

Vitamin D3 is a safe fat-soluble vitamin, even when administered in a single larger dose. Vitamin D levels remain elevated even with missed doses [20]. Vitamin D toxicity is rare and would require doses far greater than those used in this study [21].

Results

A total of 69 patients were recruited for the study. At the time of reporting the results, 27 patients had completed the full three-year trial, and 7 patients had completed two years. The dropout rate was 51% (Fig. 1), and ultimately, 34 patients were included in the final analysis. Due to recruitment challenges and participant dropout, the intended sample size of 130 patients was not reached.

All patients underwent an annual MRI, and in some cases, additional CT scans were performed for acute complaints, such as RAP episodes ($n=7$) or abdominal pain ($n=1$). No missing data.

Patient Characteristics

Patient characteristics are presented in Table 1. All patients had the first AP episode at the beginning of the trial. In all patients, pancreatitis severity was graded as either moderate or mild. There were no statistical differences between the study groups regarding age, gender, etiology or initial laboratory tests.

Chronic Pancreatitis (CP) Findings

In the final analysis, fibrosis was slightly more frequent in the low-dose vitamin D (LDVD) group ($n=4$) than in the high-dose vitamin D (HDVD) group ($n=1$), but this difference was not statistically significant ($p=0.240$).

Fewer patients in the HDVD group developed CP-related findings ($n=4$, 27%) compared to the LDVD group ($n=13$, 68%, $p=0.016$), as shown in Table 2. Only the LDVD group

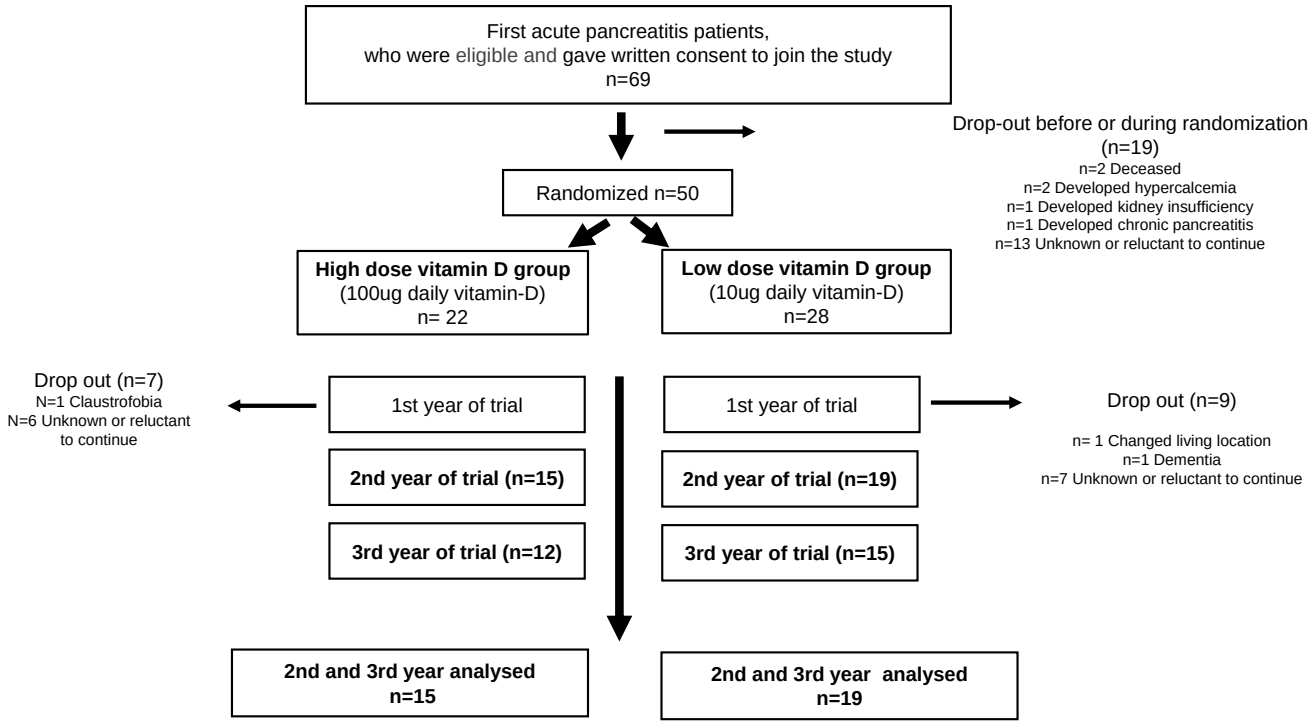


Fig. 1 Flowchart of the patients recruited and analyzed in the trial

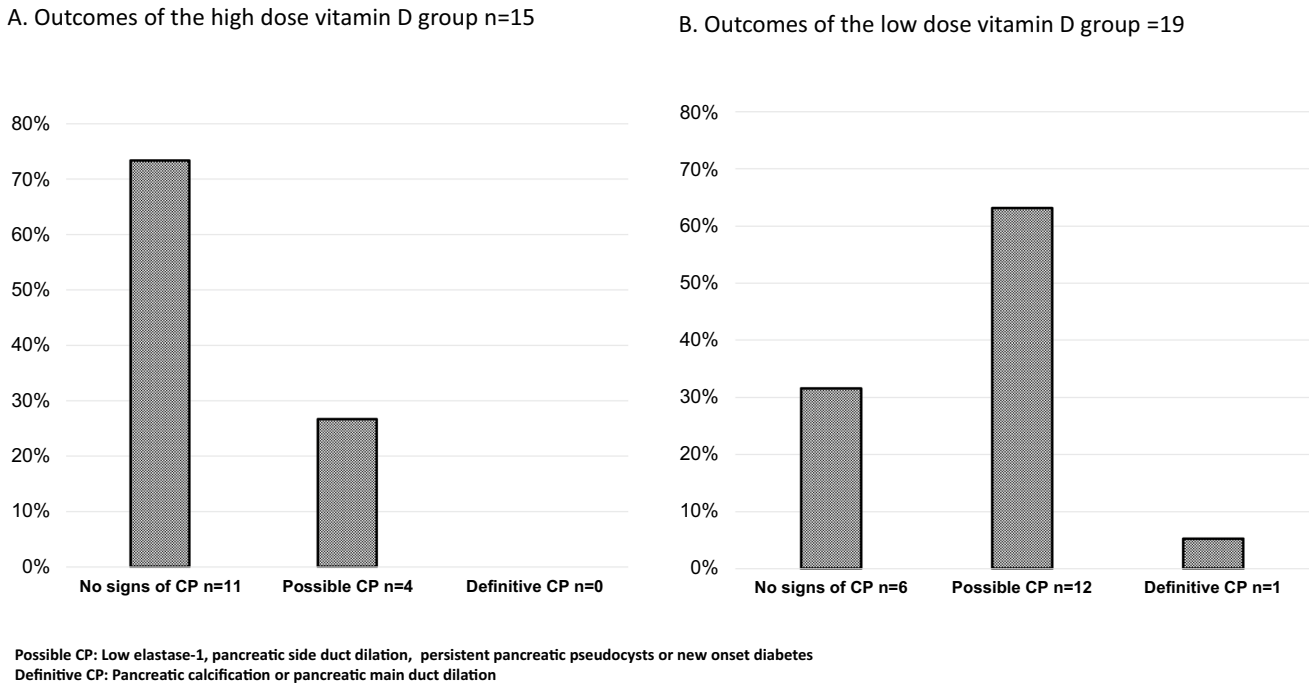


Fig. 2 Significantly fewer patients in the high-dose vitamin D group showed signs of chronic pancreatitis (CP) compared to those in the low-dose group ($p = 0.016$)

had one case of definitive CP ($p=0.367$, not statistically significant). The HDVD group exhibited significantly fewer cases of possible CP ($n=4$, 33%) compared to the LDVD group ($n=12$, 68%, $p=0.034$) (Fig. 2). Detailed findings of the trial are presented in Table 3. One patient from the HDVD group developed CP with pancreatic calcification six months after the trial.

RAP and Other Parameters

There were no statistically significant differences in the incidence of RAP between the groups: 5 patients (26%) in the LDVD group and 3 patients (20%) in the HDVD group ($p=0.66$).

In terms of exocrine pancreatic function, no patients in the HDVD group had low fecal elastase-1 (FE1) levels, while 4 patients (21%) in the LDVD group exhibited low FE1 levels. This difference was not statistically significant ($p=0.059$).

In the later follow-up two patients from the LDVD group and one from the HDVD group had RAP 1–3 years after the end of the vitamin D trial.

The LDVD group had four patients with a high HbA1c(over 48 mmol/mol) and one patient with a single high serum amylase level (210 U/l) measured. There were no elevated HbA1c or amylase levels in the HDVD group. (Table 2).

Vitamin D and Calcium Levels

The HDVD group had significantly higher vitamin D levels compared to the LDVD group. However, blood ionized calcium levels were similar between the two groups (Table 2).

Alcohol Consumption

There were no significant differences in the Alcohol Use Disorders Identification Test (AUDIT) scores between the two groups at any point during the study (Tables 1 and Table 2). While the AUDIT scores decreased in both groups over the course of the trial, this reduction reached statistical significance only in the LDVD group (7 [IQR 3–16] vs. 2 [IQR 0–4], $p=0.029$), but not in the HDVD group (10 [IQR 6–17] vs. 4 [IQR 2–12], $p=0.096$).

Quality of Life and Symptoms

Quality of life (QoL) and symptom scores did not differ significantly between the groups when comparing baseline scores to those at the end of the trial (Figs. 3 and Fig. 4).

Table 3 Individual outcomes of the randomized controlled trial following acute pancreatitis. The HDVD group received 100 µg of daily vitamin D, and the LDVD group received 10 µg of daily vitamin D

High-dose vitamin D group $n=15$	Findings	Etiology
Possible CP $n=4$	Persistent pseudocysts and atrophy	Alcohol
	Persistent pseudocysts	Alcohol and smoking
	Persistent pseudocysts	Alcohol
	Persistent pseudocysts	Alcohol
Low-dose vitamin D group $n=19$		
Definitive CP $n=1$	Atrophy, low FE1 and pancreatic calcification	Idiopathic
Possible CP $n=12$	Atrophy and new onset DM	Alcohol and smoking
	Low FE1	Efferent duct
	Persistent pseudocysts	Alcohol and smoking
	Persistent pseudocysts	Alcohol and smoking
	Atrophy and persistent pseudocysts	Alcohol
	Persistent pseudocysts	Alcohol
	Persistent pseudocysts	Idiopathic
	Atrophy, persistent pseudocysts and new onset DM	Idiopathic
	Side duct dilation	Alcohol and smoking
	Side duct dilation and low FE1	Alcohol
	Side duct dilation and low FE1	Alcohol and smoking
	Side duct dilation and new onset DM	Idiopathic

Possible CP: Low elastase-1, pancreatic side duct dilation, persistent pancreatic pseudocysts or new onset diabetes

Definitive CP: Pancreatic calcification or pancreatic main duct dilation

The LDVD group showed more chronic pancreatitis (CP) outcomes. *FE1* fecal elastase-1, *DM* diabetes mellitus, *IQR* interquartile range, *CP* chronic pancreatitis, *AUDIT* alcohol use disorders identification test, *HbA1c* glycated hemoglobin

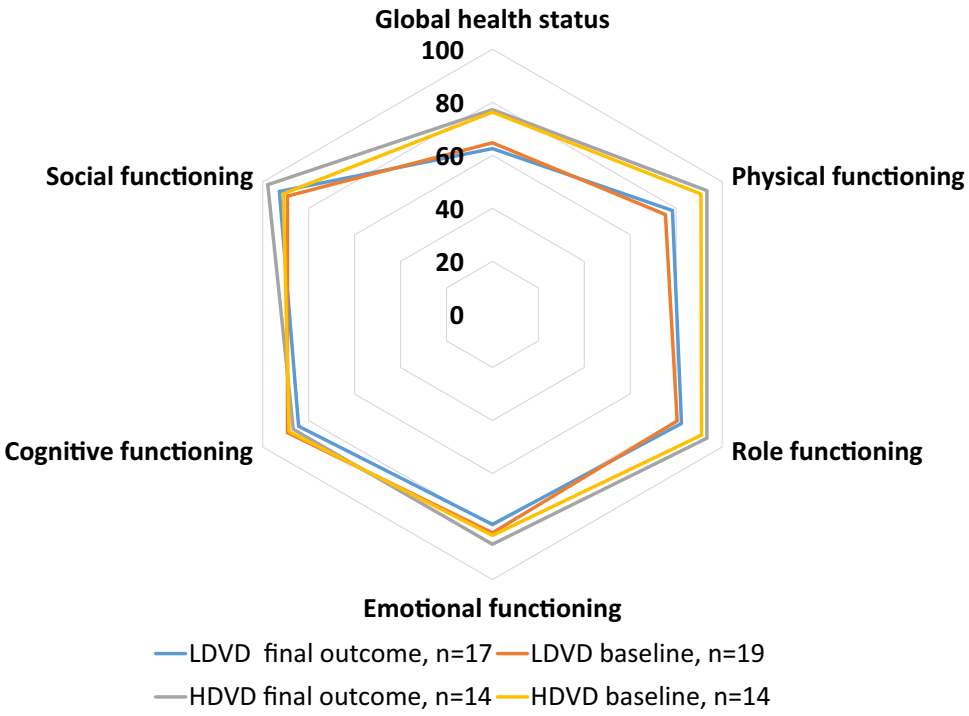
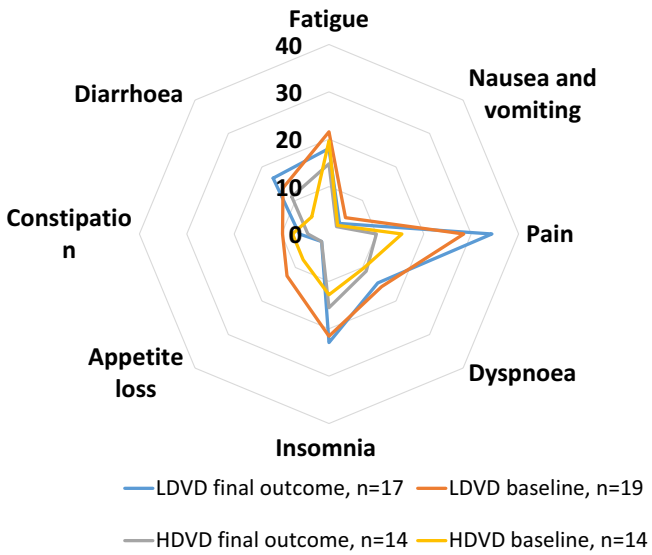


Fig. 3 EORTC QLQ-C30 quality of life scores over the course of the trial in the low-dose vitamin D (LDVD) and high-dose vitamin D (HDVD) groups. The baseline scores reflect the results at the start of the trial, 30 days after the first acute pancreatitis episode. Higher scores in QOL/functioning indicate better outcomes

A. QLQ-C30 symptom scores



B. Pan26 symptom scores

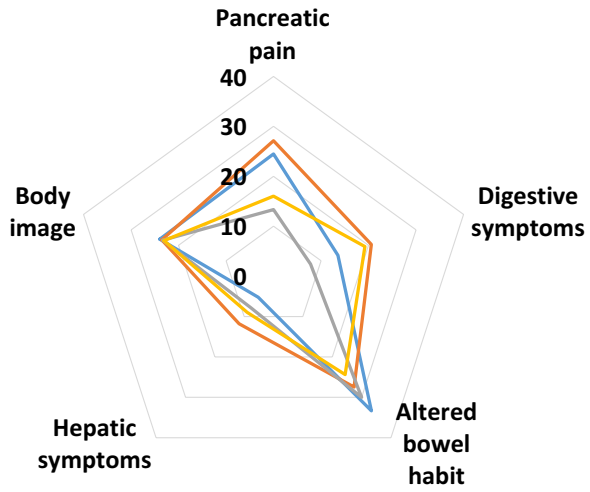


Fig. 4 EORTC QLQ-C30 and Pan26 symptom scores in the LDVD and HDVD groups during the trial. The baseline scores reflect results 30 days after the first acute pancreatitis episode. At the end of the trial, the HDVD group had a statistically lower pain score ($p=0.019$), but no significant difference in pancreatic pain score ($p=0.085$). Lower scores in symptoms represent better outcomes

At the conclusion of the trial, the LDVD group reported significantly higher pain scores on the QoL questionnaire (QLQ-C30) compared to the HDVD group (34 vs. 10, $p=0.019$), but no significant difference was observed for pancreatic pain scores (Pan26) (25 vs. 13, $p=0.08$). Other QoL and symptom scores did not differ significantly between the groups at the end of the trial.

Discussion

CP is an irreversible disease that leads to significant comorbidities and a reduced life expectancy, with no known cure. Previous studies have shown that physiological and clinically attainable concentrations of 1,25-dihydroxyvitamin D3 suppress the proliferation of pancreatic stellate cells (PSCs) and the expression of extracellular matrix proteins in mouse models [9, 10]. In the present study, our aim was to investigate whether daily vitamin D supplementation could prevent the development of CP after a first episode of AP in patients. Our initial hypothesis was that parenchymal changes indicative of fibrosis might develop following AP. We observed a slightly higher occurrence of such changes in the HDVD group compared to the LDVD group. However, this difference did not reach statistical significance, likely due to the limited sample size.

The preliminary results suggest that a high dose of vitamin D may have a protective effect against the progression of CP.

Vitamin D3, when absorbed, is biologically inactive. The liver hydroxylates it to 25-hydroxyvitamin D (vitamin D-25), which serves as the main storage form and precursor to calcitriol, the active form of vitamin D. Vitamin D-25 is a stable hormone with a half-life of approximately three weeks [11, 12], meaning that missed doses are unlikely to significantly impact vitamin D levels (20). In this study, vitamin D-25 levels were used to assess the vitamin D status of participants.

Our findings suggest that patients receiving higher doses of vitamin D after their first episode of AP exhibited fewer signs of CP, including low fecal elastase-1 (FE1) levels, persistent pseudocysts, new-onset diabetes, and side duct dilation. Notably, only the LDVD group had one case of definitive CP, according to the M-ANNHEIM criteria [13]. These findings support the hypothesis that vitamin D may play a role in preventing the progression of CP following an initial AP episode.

It is well-established that even a single episode of AP may lead to CP. The inflammatory response that follows AP often leads to pancreatic fibrosis and insufficiency. While a large number of patients develop CP without a prior history of AP, AP and RAP are significant risk factors for the development of CP [22, 23].Studies show that 4–14% of patients with AP progress to CP. Alcohol use, smoking, and episodes of severe or RAP are major risk factors for progression to CP, with risk reaching up to 50% [24–26]. Our initial estimate that 30% of patients develop chronic pancreatitis after a first acute episode have been too high.

PSCs are central to the fibrotic process in CP, with several factors known to activate them, including nicotine, alcohol, mechanical stress, and inflammation [27, 28]. Thus, suppressing PSC activity could be a key strategy for preventing the irreversible fibrosis that leads to CP. Preventive interventions for CP have traditionally focused on addressing etiological factors such as smoking cessation and alcohol reduction. To date, no specific medications have been identified to prevent CP. However, preliminary studies suggest that vitamin D may be beneficial in halting CP progression [29]. Targeting PSCs to reduce pancreatic fibrosis remains a promising avenue for CP prevention.

An earlier study examining pancreatic samples from AP patients indicated that vitamin D receptor expression might predispose individuals to pancreatic fibrosis [30]. Our study is the first randomized controlled trial (RCT) to explore the effect of vitamin D on CP progression following AP. In a 2015 study, Bläuer et al. demonstrated that PSCs in mice are sensitive to vitamin D suppression at clinically achievable levels of vitamin D [10], further supporting the potential role of vitamin D in preventing CP progression. Vitamin D deficiency is known to be prevalent in patients with CP, in part due to PEI [29]. Interestingly, our studies suggest that this deficiency may also contribute to the progression of CP.

The vitamin D doses in this study were chosen based on recommendations from the Finnish Food Authority, the Finnish Institute for Health and Welfare, and the European Food Safety Authority, with 10 µg representing the lowest recommended dose and 100 µg the highest [19]. No toxic levels of vitamin D-25 were observed in the HDVD group.

MRI was used as the primary imaging modality in this study due to its sensitivity in detecting fibrosis and ductal abnormalities, though it is less effective at identifying parenchymal calcification, a diagnostic criterion for CP. Pancreatic calcifications are optimally detected via CT scans[31]. Only patients with suspected RAP or abdominal pain underwent CT scans, which means some calcifications may have been missed. We chose MRI for its radiation-free nature and superior sensitivity for detecting early pancreatic changes compared to CT [32].

The dropout rate in our study was notably high (51%), which is consistent with challenges faced by other studies involving pancreatitis patients [33]. It is possible that the patients who dropped out had higher alcohol consumption, which may have affected their commitment to the study, this may have caused bias due to having selected patients at a lower risk for developing CP. A considerable number of patients dropped out of the study before randomization. It is possible that the psychological stress and stigma caused by AP could lead to neglecting the disease on being discharged. [34] However, as the vitamin D supplements were provided free of charge, financial constraints were unlikely to have contributed to the dropouts. Additionally, participants were not compensated for their involvement

in the study. We could not compare highdose vitamin D to a none daily vitamin D since vitamin D is recommended for everybody in Finland.

We recruited patients with mild or moderate AP, leaving those with severe pancreatitis, who may be at higher risk for developing CP. It would have been informative to examine the effect of vitamin D supplementation in this higher-risk group [26]. The main reason for having no severe pancreatitis cases, even though they were not excluded from the trial, was the lengthy hospital stays typical of these patients, which would have interfered with their ability to enrol in the study within the required timeframe (one month from the initial AP episode). Severe AP is also associated with acute kidney failure, which was an exclusion criterion for the study. Since the severity of pancreatitis is associated with the development of CP it should be mentioned that even though it did not reach significance ($p = 0.08$) the LDVD group had more mild pancreatitis than the HDVD group (Table 1) However, focusing on mild and moderate AP may also be considered a strength, as these patients represent the majority of AP cases and are more likely to be candidates for preventive interventions in routine clinical practice. [26]

Alcohol use and smoking are major risk factors for progression from acute to chronic pancreatitis [24–26], and differences in etiology or severity could influence outcomes. Although randomization aimed to balance these factors, our small sample size limits the ability to detect differences. There was a trend toward higher alcohol use in the HDVD group and more smoking and mild AP in the LDVD group, which may have introduced potential bias.

The single-center design in Finland, a high-latitude country where vitamin D deficiency has historically been common, may limit external validity. However, national nutrition policies have significantly improved vitamin D intake and status in Finnish adults over the past decade [35], meaning the population is not universally deficient. While this setting provided a controlled environment to study supplementation in a high-risk population, results may not fully apply to regions with different baseline vitamin D status. The use of low-dose vitamin D as a control was chosen because vitamin D supplementation is standard care in Finland, making a true placebo ethically challenging. Although the trial was blinded to dose allocation, awareness that vitamin D was involved could have introduced performance bias.

Due to recruitment challenges and the high dropout rate, we were unable to complete the study as originally planned. As a result, the study was discontinued and we had to deviate from the study protocol, and the final analysis was based on the 34 patients who completed two to three years of the trial. It is also possible that the study duration of two to three years was insufficient for the full development of CP [36]. The low sample size combined with the dropout rate underpowers our study and leads to non-significant results when there was a trend towards low fibrosis and definitive CP in the HDVD group.

The long recruitment period overlapped with the COVID-19 pandemic, which may have affected recruiting and follow-up adherence. These factors, combined with the small sample size, underscore the need for larger, multi-center trials to confirm these preliminary findings.

Despite these limitations, our study's strength lies in its randomized, blinded, controlled design. There were no significant baseline differences between the groups. It must be stated that the HDVD group had slightly more alcohol consumption and the LDVD group had more smoking (Table 1) but this did not reach statistical significance probably due to the low patient count.

Conclusion

A daily high-dose (100 µg) vitamin D supplementation after a first episode of AP was associated with fewer early chronic pancreatitis-related changes during a 2–3-year follow-up. While our pilot study offers promising preliminary results, larger, multi-center randomized controlled trials with longer follow-up periods are necessary to definitively establish the preventive effects of vitamin D in this context. Conducting long-term interventional trials in this patient population can be challenging.

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Author Contributions Authors M.P. and J.L. designed the study. A.A., M.U., P.P. and E.H. recruited and followed up the patients. I.R. did the radiological analysis and helped write the manuscript. J.L. supervised and funded the project. All authors interpreted the data and contributed to the writing of the paper.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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