DOI 10.4149/BLL_2024_79

Bratisl Med J 2024; 125 (8):

CLINICAL STUDY

Vitamin D in blood serum and chronic pancreatitis

Marie PRECECHTELOVA[1,2], Petr DITE[1,5], Dana BUCKOVA[2,3], Martina BOJKOVA[4,5], Bohuslav KIANICKA[2,6], David SOLIL[1,2], Jiri DOLINA[1,2]

Second Department of Internal Medicine, St. Anne's Faculty Hospital, Brno and the Faculty of Medicine, Masaryk University, Brno, Czech Republic. **bohuslav.kianicka@fnusa.cz**

ABSTRACT

Patients with chronic pancreatitis are at risk of developing malabsorption and malnutrition. Exocrine pancreatic insufficiency is accompanied by decreased serum micronutrient levels and low vitamin D levels are a frequent finding in up to 60–80% of patients. The aim of our prospective study was to investigate vitamin D in the blood serum of subjects with chronic pancreatitis with the possibility of influencing the reduced vitamin D levels with supplementation therapy.

MATERIAL AND METHODOLOGY: Fifty patients with chronic pancreatitis and 20 subjects in the control group without gastrointestinal tract diseases, including pancreatic disease, were examined. The vitamin D level in blood serum was determined. The results were evaluated according to the age distribution of subjects with pancreatic disease and according to gender. Patients with low vitamin D levels were treated for 24 weeks with a dose of 1.500.000 IU of vitamin D3 per day, and then blood serum vitamin D levels were determined.

RESULTS: In people with chronic pancreatitis, vitamin D levels were statistically significantly reduced compared to the control group. There was no statistically significant relationship of vitamin D with gender and age. Supplementation with vitamin D3 achieved an adjustment of vitamin D level to the level of the control group.

CONCLUSION: Blood serum vitamin D levels are significantly reduced in people with chronic pancreatitis. Its correction by oral vitamin D supplementation was effective. Whether this adjustment of levels will be effective also in terms of e.g. beneficial effect on fibrogenesis will require further representative studies, because the limitation of the interpretation of the results of our study is the smaller number of subjects with chronic pancreatitis *(Tab. 4, Ref. 29)*. Text in PDF www.elis.sk

KEY WORDS: chronic pancreatitis, exocrine pancreatic insufficiency, pancreatic fibrosis, vitamin D, vitamin D supplementation.

Introduction

Vitamin D is a substance that promotes calcium resorption in the proximal parts of the intestine, with the participation of free fatty acids and bile acids. Vitamin D induces osteoclast formation and activation with mobilization of calcium into bone. Together with parathyroid hormone, vitamin D stimulates the reabsorption of calcium, and to a lesser extent phosphate and magnesium, in the small intestine (1). Blood serum vitamin D is bound to a protein carrier through which it is transported to the liver where it is hydrolyzed. The final product of vitamin D formation is the formation of calcitriol. The process is mainly controlled by the amount of serum calcium and phosphorus, and parathyroid hormone plays an important role.

It is a fact that the optimal serum level of vitamin D has not yet been determined. Its deficiency is assessed by the serum level of the vitamin D metabolite calcidiol. A deficiency is defined as a value less than 50 mmol/l, insufficiency is defined by a calcidiol level between 50.0–75.0 mmol/l and the optimal level is 75.0–200.0 mmol/l (2).

The effect of vitamin D in the human body is very broad. It positively influences the effect of pro-inflammatory cytokines, inhibits angiogenesis, or participates in the function of the immune system. Therefore, it is also important to observe the conditions that can be both the cause and the consequence of vitamin D deficiency in the human body. Such conditions, among many others, include chronic pancreatitis (3). A meta-analysis of 9 studies looking at the prevalence of vitamin D deficiency in people with chronic pancreatitis found a statistically significant prevalence of vitamin D deficiency ($p<0.05$) in a sample of 465 people compared to healthy individuals (4). The answer to the question of what causes this deficit in people with chronic pancreatitis is complicated. As pointed out by the authors from Denmark, vitamin D levels in

[1]Department of Internal Gastroenterology, University Hospital Brno, Brno, Czech Republic, [2]Faculty of Medicine, Masaryk University, Brno, Czech Republic, [3]Institute of Laboratory Medicine – Department of Clinical Biochemistry, Faculty Hospital Brno, Brno, Czech Republic, [4]Internal Cardiology Clinic – Department of Gastroenterology, Faculty Hospital Ostrava, Czech Republic, [5]Faculty of Medicine, University of Ostrava, Department of Internal Medicine, Ostrava, Czech Republic, and [6]Second Department of Internal Medicine, St. Anne's Faculty Hospital, Brno and the Faculty of Medicine, Masaryk University, Brno, Czech Republic

Address for correspondence: Bohuslav KIANICKA, Prof, MD, PhD, Second Department of Internal Medicine, St. Anne's Faculty Hospital, Brno and the Faculty of Medicine, Masaryk University, Brno, Pekarská 53, Czech Republic
Phone: 543 182 252

people with chronic pancreatitis are influenced by a number of factors, such as the presence of secondary hyperparathyroidism, dietary measures, climatic influences, or pancreatic malnutrition and malabsorption (5).

Vitamin D is a steroid hormone that, as mentioned above, regulates the body's calcium and phosphorus levels. In recent years, its pleiotropic effect has been described, including regulation of cell proliferation, differentiation, apoptosis and autophagy, antagonizing inflammation, fibrosis and carcinogenesis (6). It should be taken into account that vitamin D is a promising drug in the therapy of many non-skeletal conditions, such as cardiovascular diseases, diabetes mellitus, infections, cancer, or autoimmune diseases (7, 8, 9). Still, some correlations between vitamin D and chronic pancreatitis are controversial (10). However, it is clear that vitamin D analogues suppress the stroma in both chronic pancreatitis and pancreatic cancer through inhibition of pancreatic stellate cell activation (11, 12).

In the pathophysiology of chronic pancreatitis, the pathological features are due to inflammatory cell infiltration, pancreatic fibrosis, and acinar cell atrophy.

In our prospective observational study, we evaluated vitamin D levels in people with chronic pancreatitis in relation to parameters used in the examination and monitoring of people with chronic pancreatitis, such as the monitoring of exocrine pancreatic insufficiency, Body Mass Index, serum potassium levels, parathyroid hormone levels and calcemia.

Administration of standard recommended doses of vitamin D was clinically indicated and implemented as a commonly used treatment in persons with low serum vitamin D levels. Cholecalciferol (vitamin D3) was administered as oral drops (1 drop = 500 IU) at a dose of 3 drops per day – 1.500.000 IU for 3 months, up to 6 months if no increase in serum vitamin D levels was achieved. To limit the effect of seasonal changes in vitamin D levels in the human body, the study was conducted over the time interval of December 2022 to May 2023, i.e. 6 months.

Material and methodology

Criteria for inclusion in clinical follow-up:

a) diagnosis of chronic pancreatitis according to the new mechanistic definition (13) and according to the 2019 diagnostic criteria (14),
b) age 18–70 years,
c) the patient has not undergone pancreatic resection,
d) the patient has not undergone gastric or small bowel resection,
e) l iver function tests and renal function within normal limits.

Exclusion criteria:

a) individuals under 18 years of age,
b) suspected pancreatic cancer,
c) parathyroid disease,
d) primary malabsorption syndrome,
e) alcoholics,
f) use of drugs affecting the resorption and/or metabolism of vitamin D.

At the time of the study, none of the subjects reported abdominal pain.

In the evaluated cohort, a total of 70 individuals were included, including 50 individuals with a diagnosis of chronic pancreatitis who were referred to the pancreatology outpatient clinic of our department for examination and dispensation. The 20 persons included in the control group were individuals who did not report any dyspeptic disorders, had no history of gastrointestinal tract disease, diabetes mellitus, parathyroid disease, liver disease or chronic kidney disease. In the group of subjects with chronic pancreatitis, 19 women and 31 men were included. The mean age of the chronic pancreatitis group was 62.2 years (52–80 years), the mean age of the control group was 50 years. The diagnosis of chronic pancreatitis was made by imaging methods (abdominal sonography, CT scan, endoscopic sonography, or endoscopic retrograde cholangio-pancreatography). Pancreatic exocrine function was assessed by fecal elastase-1 determination. Inclusion and follow-up of patients in the study population was limited to an interval of 6 consecutive calendar months, in order to limit the influence of seasonal variations on blood serum vitamin D levels. During the period of vitamin D administration, the patients did not change their therapy, during which the blood serum vitamin D levels were determined, including the administration of pancreatin.

Vitamin D substitution in the form of cholecalciferol was administered to those with low vitamin D levels. The drug was administered in the form of oral drops, where 1 drop contains 500 IU of vitamin D3. Three drops per day – 1.500.000 IU of vitamin D3 – were administered for 3 months, and in case of inadequate blood serum vitamin D levels, vitamin D was administered for a total of 6 months. Blood for determination of biochemical parameters was always drawn in the morning, on an empty stomach, before vitamin D medication administration. A control collection was performed 3 months after vitamin D administration; if there was no increase in serum vitamin D levels, the collection was repeated 6 months after the initiation of the medication.

Results

Table 1 shows the characteristics of selected variables and the comparison between the chronic pancreatitis group and controls. The difference in the gender category is statistically evaluated using Fisher's exact test, and the non-parametric Mann–Whitney test was used for further statistical evaluation. Differences in serum

Tab. 1. Characteristics of persons with chronic pancreatitis and control groups by sex and age.

	Total	Men	Women	Average age	Median	SD
Chronic pancreatitis	50	31 (62 %)	19 (38 %)	62.2 (29–80)	65.5	13.8
Control group	20	8 (40 %)	12 (60 %)	50.0 (19–76)	46.0	16.3

vitamin D levels when the study population of people with chronic pancreatitis was divided according to age into 3 groups, into the group of people aged less than 50 years (n=11), the group aged 50-69 years (n=17) and the group aged over 70 years (n=22) were statistically insignificant (p=0.290).

When evaluating the biochemical parameters of patients with chronic pancreatitis, statistically significant differences were found in the determination of triglyceridemia (p=0.002), which is statistically significantly higher in people with chronic pancreatitis than in controls, a similar finding applies to the value of glycemia (p=0.001). Total protein is statistically significantly lower than in the control group (p=0.011). Table 2

Other biochemical parameters – amylasemia, lipase albuminemia, cholesterolemia, aminotransferase values, calcemia – are not different from controls.

Average parathyroid hormone level 3.1 (norm 1.58–6.29)

Average selenium level –1.0 (norm 0.7–1.24)

Average zinc level 10.8 (norm 9.2–18.4)

Serum selenium and zinc levels are within normal limits.

BM – mean in people with chronic pancreatitis 27.1 vs controls 28.8 – p=0.073

Blood serum vitamin D levels in the control group of healthy subjects and the group of patients with chronic pancreatitis were statistically significantly reduced in the patients with chronic pancreatitis (p<0.001).

After treatment with vitamin D at a dose of 1.500.000 IU per person for 24 weeks, a statistically significant increase in blood serum vitamin D was found, corresponding to the level of the control group of healthy subjects (Tab. 3).

Comparison of serum vitamin D levels in patients with chronic pancreatitis, divided according to age into 3 groups, showed no statically significant difference between the group of patients younger than 50 years, the group aged 50–70 years and the group of patients older than 70 years (p=0.290).

The vitamin D level in the group of people with chronic pancreatitis and evidence of exocrine pancreatic insufficiency (FE-1<100) was reduced (37.4 mmol/l), compared to the group of people with chronic pancreatitis and normal fecal elastase level (48.5 mmol/l) – FE-1 level >100. The difference is statistically insignificant at p 0.423 (Tab. 4.)

Tab. 2. Spectrum of investigated biochemical parameters – pathological findings.

CHP/Controls	Mean	Median	SD	p
Glycaemia	(6.4–5.0)	(5.8–5.1)	(1.5–0.4)	<0.001
Triacylglycerolemia	(1.5–1.0)	(1.3–0.9)	(0.8–0.4)	<0.002
Total protein	(70.9–73.3)	(71.6–71.3)	(4.2–3.0)	0.011

Tab. 3. Vitamin D levels in persons with chronic pancreatitis before and after vitamin d treatment.

	n	Mean	SD	Scope	p
Before treatment	50	48.0	17.0	19–100	
After treatment	50	88.3	27.9	27–171	<0.001
Control group	20	135.5	110.2	74–151	

Discussion

Reduced exocrine pancreatic secretion results primarily in malnutrition and is associated poor quality of life. Reduced serum magnesium or zinc levels are often reported in association with PEI. Reduced vitamin D levels are reported to range from 22.0% to 86.5% (15). Zhang and Gao found a statistically significant reduction in vitamin D levels, especially in a group of patients with the alcoholic form of chronic pancreatitis (16). Comparison of vitamin D levels in the so-called definitive form of chronic pancreatitis and in a group of patients with early form of chronic pancreatitis showed that in the early form of chronic pancreatitis, vitamin D levels are reduced, but this reduction is significantly lower in the definitive form of the disease than in the advanced form (17).

A Danish study involving 115 individuals with chronic pancreatitis demonstrated that micronutrient deficiency is one particularly common finding (15). A European study of 211 patients with chronic pancreatitis published in 2018 found 56% to be vitamin D deficient (18). In a study from the USA, even 62.5% of patients with chronic pancreatitis were vitamin D deficient; 67.3% of the 88 patients were male, with a preponderance of smokers (19).

In our study, we demonstrated a statistically significant decrease in vitamin D levels in subjects with chronic pancreatitis, compared to the control group. However, we did not find a reduction in zinc and selenium levels in our cohort, although some individuals had levels below the norm. Among biochemical parameters, serum total protein level was significantly lower, while triacylglycerolemia and glycemia levels were statistically increased compared to controls.

Patients with chronic pancreatitis had statistically significantly lower vitamin D levels before vitamin D treatment compared to the control group. A statistically significant increase in values was demonstrated after vitamin D treatment /p < 0.001/, when the total vitamin level in blood serum was equal to the serum level of the control group. The effect of vitamin D therapy in relation to gender was without statistical significance.

Exocrine pancreatic insufficiency in our cohort was evaluated by fecal elastase-1 (FE-1). In the control group with normal FE-1 levels, the mean serum vitamin D level was 135.5 mmol/l, whereas in subjects with chronic pancreatitis, the mean serum vitamin D level was 48.5mmol/, if fecal elastase-1 levels were not indicative of significant exocrine pancreatic insufficiency. In patients with FE-L findings of exocrine insufficiency, the serum vitamin D level was 37.4 mmol/l.

It is evident that nutritional management in people with chronic pancreatitis is an important part of the comprehensive therapy of chronic pancreatitis and its tropical form (20, 21). The route by which vitamin D is administered is not essential; both oral and

Tab. 4. Vitamin d levels in control groups with normal fecal elastase and chronic pancreatitis – fecal elastase-1 reduced < 100.

Vitamin D mmol/l	Mean	Median	SD	
CHP FEnorm	48.5	47.3	15.9	p=0.423
CHP FE L<100	37.4	44.0	18.4	
Control group	90.5	110.2	29.6	

parenteral forms are effective (22). In our study, we confirmed that oral administration of vitamin D at a dose of 1,500,000 IU for 6 months is effective and leads to normalization of serum vitamin levels.

The mechanism of action of vitamin D in people with chronic pancreatitis is multifaceted. The application of vitamin D has an anti-inflammatory effect and favorably affects the process of tissue fibrotization. A study published as early as 2013 by Ding et al (23) showed that the vitamin D analogue calcipotriol has a significant antagonizing effect, via TGF-beta, on the controlled expression of the pre-fibrotic gene and on the influence of liver fibrotization.

Vitamin D regulates the inflammatory process in tissues of some organs through the p38 MAPK pathway, inhibition of NF-kappaB, and through prostaglandin activation (24, 25, 26).

In the clinic, in individuals with chronic pancreatitis, decreased vitamin D levels are accompanied by osteoporosis (27).

Despite these findings, however, it is still not conclusive whether vitamin D deficiency is a true risk factor for the development of chronic pancreatitis. However, this does not change the fact about the therapeutic status of vitamin D in patients with chronic pancreatitis and its complications (28, 29). However, it is a fact that at present, despite all of the above, there is still not enough information on the optimal route of administration of vitamin D, as well as on the optimal dosage and time distribution of individual doses of vitamin D.

Conclusion

Reduced vitamin D levels are a common finding in people with chronic pancreatitis and are associated with a risk of adverse disease outcomes. However, there is no clear evidence that low vitamin D levels are an initiating factor for the development of pancreatitis.

Vitamin D has been confirmed as a substance that affects the prognosis of chronic pancreatitis, influences the function of a number of organs, and has a beneficial effect on the inflammatory processes of the body. Vitamin D and its analogues inhibit the activity of pancreatic stellate cells, reduce the process of pancreatic fibrosis. Vitamin D thus becomes a substance that may have a significant therapeutic antifibrotic effect. Therefore, high-quality, prospective studies should be initiated to confirm this antifibrotic effect of vitamin D unequivocally in clinical practice.

References

1. Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmelit G. Vitamin D: Metabolism, molecular mechanism of action, and pleiotropic effects. Physiol Rev 2016; 96 (1): 365–408. https://doi:10.1152/physrev.00014.2015.

2. Broulík P, Kočí K. Úloha vitaminu D pro lidský život. Medicína po promoci 2021; 22 (1): 32–77.

3. Martinez-Moneo E, Stigliano S, Hedstrom A et al. Deficiency of fat-soluble vitamins in chronic pancreatitis: A systematic review and meta-analysis. Pancreatology 2016; 16 (6): 988–984. https://doi:10.1016/j.pan.2016.09.008.

4. Hoogenboom SA, Lekkerkerker SJ, Fockens P, Boermeester MA, van Hooft JE. Systematic review and meta-analysis on the prevalence of vitamin D deficiency in patients with chronic pancreatitis. Pancreatology 2016; 16 (5): 800–806. https://doi:10.1016/j.pan.2016.07.010.

5. Olesen SS, Poulsen JL, Vestergaard P, Drewes AM. Vitamin-D deficiency in patients with chronic pancreatitis – Prevalence and pitfalls. Pancreatology 2017; 17 (1): 22–23. https:// doi:10.1016/j.pan.2016.10.007.

6. Golpour A, Bereswill S, Heimesaat MM. Antimicrobial and immune-modulatory effects of vitamin D provide promising antibiotics-independent approaches to tackle bacterial infections- lesson learnt from a literature survey. Eur J Microbiol Immunol 2019; 9 (3): 80–87. https://oid10.1556/1886.2019.00014.

7. Grant WB, Lahore H, McDonell SL et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 2020; 12 (4): 988. https://doi:10.3390/nu12040988.

8. Harrison SR, Li D, Jeffery LE, Raza K, Hewison M. Vitamin D, autoimmune disease and rheumatoid arthritis. Calcif Tissue Int 2020; 106 (1): 58–75. https://doi:10.1007/s00223-019-00577-2.

9. de la Guía – Galipienso F, Martínez-Ferran M, Vallecillo N, Lavie CJ, Sanchis-Gomar F, Pajera-Galeano H. Vitamin D and cardiovascular health. Clin Nutr 2021; 40 (5): 2946–2957. https:// doi:10.1016/j.clnu.2020.12.025.

10. Martínez-Maneo E, Stigliano S, Hedström A et al. Deficiency of fat-soluble vitamins in chronic pancreatitis: A systematic review and meta-analysis. Pancreatology 2016; 16 (6): 988–994. https://doi:10.1016/j.pan.2016.09.008.

11. Kang ZS, Wang C, Han XL, Du JJ, Li YY, Zhang C. Design, synthesis and biological evaluation of non-secoteroidal vitamin D receptor ligand bearing double side chain for the treatment of chronic pancreatitis. Eur J. Med Chem 2018; 146: 541–553. https://doi:10.1016/j.ejmech.2018.01.073.

12. Wallbaum P, Rohde S, Ehlers L et al. Antifibrogenic effects of vitamin D derivatives on mouse pancreatic stellate cells. World J Gastroenterol 2018; 24 (2): 170–178. https://doi:10.3748/wjg.v24.i2.170.

13. Whitcomb DC, Frulloni L, Garg P et al. Chronic pancreatitis: an international draft consensus proposal for a new mechanistic definition. Pancreatology 2016; 16 (2): 218–224. https:// doi:10.1016/j.pan.2016.02.001.

14. Shimizu K, Ito T, Irisawa A et al. Evidence-based clinical practice guidelines for chronic pancreatitis 2021. J Gastroenterol 2022; 57 (10): 709–724. https://doi:10.1007/s00535-022-01911-6.

15. Joker-Jensen H, Mathiasen AS, Kohler M, Rasmussen HH, Drewes AM, Olesen SS. Micronutrient deficits in patients with chronic pancreatitis: prevalence, risk factors and pitfalls. Eur J Gastroenerol Hepatol 2020; 32 (10): 1328–1334. https://doi:10.1097/MEG.0000000000001866.

16. Zhang M, Gao R. Vitamin D: A potential star for treating chronic pancreatitis. Front Pharmacol 2022; 13: 902639. https://doi:10.3389/fphar.2022.902639.

17. Zhang J, Fan H, Gross M et al. Progressive reduction in circulating levels of carotenoids and other micronutrients in patients with chronic pancreatitis. Pancreatology 2022; 22 (8): 1126–1133. https://doi:10.1016/j.pan.2022.09.243.

18. Stigliano S, Waldthaler A, Martinez-Moneo E et al. Vitamins D and K as factors associated with osteopathy in chronic pancreatitis: A prospective multicentre study (P-BONE study). Clin Transl Gastroenterol 2018; 9 (10): 197. https://doi:10.1038/s41424-018-0066-8.

19. Min M, Patel B, Han S et al. Exocrine pancreatic insufficiency and malnutrition in chronic pancreatitis: Identification, treatment and consequences. Pancreas 2018; 47 (8): 1015–1018. https://doi:10.1097/MPA.0000000000001137.

20. Bang UC, Brandt L, Befield T, Jensen JEB. Changes in 1, 25-dihydroxyvitamin D and 25- hydroxyvitamin D are associated with maturation of regulatory T lymphocytes in patients with chronic pancreatitis: a randomized controlled trial. Pancreas 2012; 41 (8): 1213–1218. https://doi:10.1097/MPA.0b013e31824da377.

21. Reddy SVB, Ramesh V, Bhatia E. Double blind randomized control study of via intramuscular vitamin D supplementation in tropical calcific pancreatitis. Calcif Tissue Int. 2013; 93 (1): 48–54. https://doi:10.1007/s00223-013-9726-6.

22. Wiese M, Gartner S, Doller J et al. Nutritional management of chronic pancreatitis: A systematic revue and meta-analysis of randomized controlled trials. J Gastroenterol Hepatol 2021; 36 (3): 588–600. https://doi:10.1111/jgh.15230.

23. Ding N, Yu RT, Subramanian N et al. A vitamin D receptor/SMAD genomic circuit gates hepatic fibrotic response. Cell 2013; 153 (3): 601–613. https://doi:10.1016/j.cell.2013.03.028.

24. Derakhsanian H, Djazayery A, Javanbakht MH et al. Vitamin D down-regulates key genes of diabetes complications in cardiomyocyte. J Cell Physiol 2019; 234 (11): 2352–2358. https://doi:10.1002/jcp.28743.

25. Yao B, He J, Yin X, Shi Y, Wan J, Tian Z. The protective effect of lithocholic acid on the intestinal epithelial barrier is mediated by the vitamin D receptor via a SIRT1/Nrf2 and NF-kB dependent mechanism in CaCo-2 cells. Toxicol Let 2019; 316: 109–118. https://doi:10.1016/j.toxlet.2019.08.024.

26. Cimmino G, Morello A, Conte S et al. Vitamin D inhibits tissue factor and CAMs expression of oxidized low-density lipoproteins-treated human endothelial cells by modulating NF-Kb pathway. Eur J Pharmacol 202; 885: 173422. https://doi:10.1016/j.ejphar.2020.173422.

27. Duggan SN, Smyth ND, O´Sullivan M, Feehan S, Ridgway PF, Conlon KC. The prevalence of malnutrition and fat-soluble vitamin deficiencies in chronic pancreatitis. Nutr Clin Pract 2014; 29 (3): 348–354. https://doi:10.1177/0884533614528361.

28. Berger M, Shenkin A, Schweinlin A et al. ESPEN micronutrient guideline. Clin Nutr 2022; 41 (6): 1357–1424. https://doi:10.1016/j.clnu.2022.02.015.

29. Greer JB, Greer P, Samdhu BS et al. Nutrition and inflammatory biomarkers in chronic pancreatitis patients. Nutr Clin Pract 2019; 14 (3): 387–399. https://doi:10.1002/ncp.10186.

Received January 7, 2024.
Accepted February 14, 2024.