Idiopathic chronic intestinal pseudo-obstruction syndrome is strongly associated with low serum levels of vitamin D

Alba Panarese[a], Elton Dajti[b,c], Leonardo Henry Eusebi[b,c], Amanda Vestito[c] and Rocco Maurizio Zagari[b,d]

Idiopathic chronic intestinal pseudo-obstruction (CIPO) is associated with intestinal inflammation and malabsorption and may cause serum vitamin D deficiency. We aimed to assess whether there is an association between idiopathic CIPO and serum levels of 25-hydroxy-vitamin D. Consecutive patients with confirmed diagnosis of idiopathic CIPO were prospectively enrolled and matched with healthy controls by gender, age, and BMI. Median serum level of 25-hydroxy-vitamin D of patients with CIPO was compared with that of healthy subjects using the Wilcoxon signed-rank test for matched samples. A total of 35 patients with CIPO and 35 matched healthy subjects were enrolled. All patients with CIPO had a 25-hydroxy-vitamin D deficiency with serum levels <12 ng/ml. The median serum level of vitamin D was significantly lower in patients with CIPO than in healthy controls (5.7 vs. 29.7 ng/ml, $P < 0.0001$). Serum level of vitamin D was not associated with gender ($P = 0.27$), age ($P = 0.22$), BMI ($P = 0.95$), high (>10 000 × ml) WBC count ($P = 0.08$), or high (>5 mg/l) C-reactive protein ($P = 0.87$) among patients with CIPO. CIPO seems to be strongly associated with low serum levels of 25-hydroxy-vitamin D. Eur J Gastroenterol Hepatol 36: 584–587

Introduction

Idiopathic chronic intestinal pseudoobstruction (CIPO) syndrome is a rare disease characterized by derangement of gastrointestinal propulsive motility that causes intestinal failure with variable degree of severity [1–3]. The pathogenesis of idiopathic CIPO is not well defined [2,4,5]. This syndrome may be due to alterations of enteric and extrinsic nervous system, interstitial cells of Cajal and smooth muscle cells, causing neuropathy, mesenchymopathy, myopathy or mixed forms [4,6]. There are three main phenotypes of idiopathic CIPO: predominant neuropathy (RAD21-related or SGO-1-related, with neuronal alterations to the interstitial cells of Cajal), myopathy (ACTG2-dependent) and neuro-myopathy caused by mitochondrial dysfunction (TYMP-, POLG-, and LIG3-related) [7]. From a clinical point of view, patients with CIPO usually present with recurrent intestinal subocclusive episodes, significant weight loss and severe malnutrition. Patients are often unable to undertake oral nutrition, with serious consequences on morbidity and mortality, and therefore require parenteral nutrition [3,4]. Most often, idiopathic CIPO remains unrecognized for long time, so that patients almost invariably undergo repeated, useless and potentially dangerous surgical procedures.

The diagnosis of CIPO requires several investigations to rule out any mechanical gastrointestinal obstruction causing a secondary CIPO. It is very important to identify the phenotype of the disease and quickly recognize and treat complications, including malnutrition and intestinal bacterial overgrowth [6]. An early diagnosis of idiopathic CIPO improves quality of life because a timely adoption of the necessary therapies reduces the damage caused by chronic inflammation. Nutritional, pharmacological and surgical therapies are often unsatisfactory, and their long-term outcome is poor in most patients [7].

The association between idiopathic CIPO and serum levels of 25-hydroxy-vitamin D is not clear. The reduced intestinal motility, impairment of the intestinal environment and chronic inflammation due to slowed intestinal transit may cause malabsorption of various macro and micronutrients that could lead to serum 25-hydroxy-vitamin D deficiency [2–4,6]. On the other hand, 25-hydroxy-vitamin D deficiency may negatively affect the gut microbiome, the mucosal immunity and the intestinal permeability and motility, thus contributing to the severity of disease. A better knowledge of the association between idiopathic CIPO and serum levels of 25-hydroxy vitamin D may help to reduce the disease severity, and to better understand the pathogenesis of CIPO. Therefore, the aim of this study was to assess the association between idiopathic CIPO and serum levels of 25-hydroxy-vitamin D.

European Journal of Gastroenterology & Hepatology 2024, 36:584–587

Keywords: 25-hydroxy vitamin D, idiopathic chronic intestinal pseudoobstruction, malabsorption

[a]Division of Gastroenterology and Digestive Endoscopy, Department of Medical Sciences, Central Hospital – Azienda Ospedaliera, Taranto, [b]Department of Medical and Surgical Sciences, University of Bologna,[c]Gastroenterology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna and [d]Esophagus and Stomach Organic Diseases Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

Correspondence to Rocco Maurizio Zagari, Esophagus and Stomach Organic Diseases Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Department of Medical and Surgical Sciences, University of Bologna, Via Massarenti n. 9. 40138 Bologna, Italy

Tel: +39 051 2145704; e-mail: roccomaurizio.zagari@unibo.it

Received 26 November 2023 **Accepted** 18 February 2024.

Materials and methods

This is a prospective matched case-control study performed in the Division of Gastroenterology and Digestive Endoscopy of Taranto, a tertiary center dedicated to rare diseases in Southern Italy. Consecutive patients with obstructive bowel symptoms and radiological evidence of small bowel dilation in the absence of obstructive disease were considered eligible for the study when the diagnosis of idiopathic CIPO was confirmed [2].

Exclusion criteria were age <18 years, recent oral intake of vitamin D, significant comorbidities such as cardiac, respiratory or chronic renal insufficiency, neoplasia, metabolic or endocrine diseases, myogenic diseases (i.e. scleroderma, amyloidosis and myotonic dystrophy dermatomyositis), use of drugs including opiates, antihypertensive agents, iron preparations, tricyclic antidepressants, anticholinergics or dopaminergics and pregnancy.

The control group included 35 healthy subjects recruited from a population-based cohort who underwent routine clinical exams in our center to check their healthy status. The study was approved by the Research Ethics Committee of the Oncological Institutes of Apulia. Signed informed consent was obtained from all participants.

Serum 25-hydroxy-vitamin D measurement

Samples of 10 ml of peripheral venous blood were collected from patients with CIPO and healthy controls after a fasting of 8 h. Samples were collected in serum tubes and 3.2% trisodium citrate anticoagulated tubes, placed upright to prevent shaking. The tubes were centrifuged at 2000 rpm for 10 min to obtain serum and platelet-rich plasma. The platelet-rich plasma was again centrifuged at 2000 rpm for 10 min to obtain platelet-poor plasma. Both serum and platelet-poor plasma samples were stored at -80 °C. The analyses were performed within 12 months. Total serum 25-hydroxy-vitamin D was measured using a chemiluminescent immunoassay on an autoanalyzer (Liaison, Diasorin, Saluggia, Italy). The 25-hydroxy-vitamin D level was categorized using a standardized cut-off (deficiency <20 ng/ml, insufficiency from 20 to 29 ng/ml, sufficient ≥30 ng/ml) [8].

Statistical analysis

The sample of patients included all subjects diagnosed with CIPO in our center since 2016. Patients with CIPO were matched with healthy subjects by gender, age and BMI using the nearest neighbor matching algorithm implemented in MatchIt [9]. Continuous variables were reported as median and interquartile range (IR), while categorical variables were described as percentages. Continuous variables were compared using the Wilcoxon signed-rank test for matched samples or the Mann–Whitney test for independent groups, if appropriate. Categorical variables were compared using the McNemar's test for matched samples. We assessed the association between serum 25-hydroxy-vitamin D levels and age and BMI in patients with CIPO using the Spearman's correlation. A *P*-value -0.05 was considered statistically significant. All statistical analyses were performed using STATA version 16 software (Stata Corp., College Station, Texas, USA).

Results

Thirty-nine consecutive patients with a diagnosis of idiopathic CIPO were eligible to be included in the study. Of these, four patients were excluded due to a previous supplementation of vitamin D (*n* = 3) or severe chronic kidney disease (*n* = 1). Finally, a total of 35 patients with CIPO and 35 healthy subjects were enrolled (Fig. 1). The median age of patients with CIPO was 36 years, 19 (54.3%) were males and the median BMI was 22.5 kg/m^2. There was no difference between the CIPO group and healthy subjects in terms of age, gender and BMI. Table 1 shows the characteristics of patients with CIPO and healthy controls.

All patients with CIPO had delayed transit colonic time, abdominal pain and constipation. Other frequent gastrointestinal symptoms were abdominal distension (*n* 29, 82.9%) and vomiting (*n* 22, 62.9%). In addition, 16 (45.7%) patients had pneumonia and 10 (29%) patients had intestinal failure. Regarding the nutritional status, 20 (57.8%) patients had malnutrition, 5 (14.3%) patients had low serum levels of folate (<3.5 mg/ml) and 2 (5.7%)

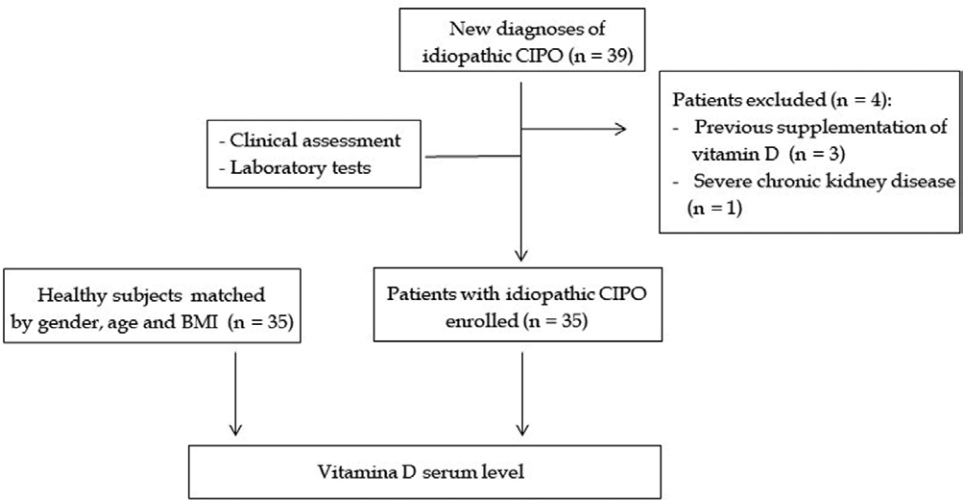

Fig. 1. Study flowchart. CIPO: chronic intestinal pseudoobstruction.

Table 1. Characteristics of patients with chronic intestinal pseudoobstruction and healthy subjects

	Healthy controls (n = 35)	Patients with CIPO (n = 35)	P-value
Age (year), median (interquartile range)	36 (20–61)	36 (20–61)	0.32
Gender, male (%)	19 (54.3)	19 (54.3)	1
BMI (kg/m^2), median (interquartile range)	21.9 (20.6–23.5)	22.5 (19–24.2)	0.44

CIPO, chronic intestinal pseudoobstruction.

Table 2. Association between serum vitamin D levels and gender, age, BMI, high white cell count, and C-reactive protein value in 35 patients with chronic intestinal pseudoobstruction

	Patients, n	Serum level vitamin D (ng/ml) median (interquartile range)	P-value
Gender			0.27
Female	16	6.3 (5.1–7.4)	
Male	19	5.3 (4.4–7.3)	
White blood cells (count × ml)			
<10 000	17	6.6 (5.2–7.6)	
>10 000	18	5.2 (4.7–6.2)	0.08
C-reactive protein value (mg/l)			0.87
<5	6	5.8 (5–6.6)	
>5	29	5.7 (4.8–7.3)	
		Spearman's coefficient	
Age (years)		0.21	0.22
BMI (kg/cm^2)		0.01	0.95

patients had low serum albumin (<3.12 gr/dl); none of the patients with CIPO had bone fractures.

All patients with CIPO had 25-hydroxy-vitamin D deficiency with serum level of vitamin D <12 ng/ml. The median serum level of 25-hydroxy-vitamin D was significantly lower in patients with CIPO (5.7, interquartile range 4.1–91, ng/ml) than in healthy controls (29.7, interquartile range 21.7–38.9, ng/ml) ($P < 0.0001$).

Of the 35 patients with CIPO, 18 (51.4%) had high (>10 000 × ml) white blood cell count and 29 (82.9%) high (>5 mg/l) C-reactive protein.

Among patients with CIPO, serum level of 25-hydroxy-vitamin D was not associated with gender ($P = 0.27$), age ($P = 0.22$), BMI ($P = 0.95$), high (>0.000 × ml) white blood cell count ($P = 0.08$) and high (>5 mg/l) C-reactive protein ($P = 0.87$) (Table 2).

Discussion

This study showed that idiopathic CIPO is strongly associated with low serum levels of 25-hydroxy-vitamin D. Among patients with CIPO, no association was found between serum 25-hydroxy vitamin D level and gender, age, BMI or markers of inflammation including high white blood cell count or C-reactive protein.

To our knowledge, this is the first study assessing the association between CIPO and serum vitamin D levels. Our finding is in line with a previous study showing that low levels of vitamin D were associated with impaired intestinal motility and chronic functional constipation [8]. Similarly, low levels of vitamin D have been reported in other immune-mediated disorders including systemic sclerosis, autoimmune gastritis and inflammatory bowel disease [9–13].

Indeed, the design of our study does not allow to clearly establish whether vitamin D deficiency in CIPO is a consequence of malnutrition or if it plays a pathogenetic role in the severity of disease; however, we cannot exclude that vitamin D deficiency may be both a consequence of malnutrition and affect the severity of CIPO.

The deterioration of bowel function caused by CIPO [1–4,6] could impair the absorption of 25-hydroxy-vitamin D and lead to a vitamin D deficiency. Also, intestinal inflammation may play a role in the malabsorption of vitamin D; in fact, most patients with intestinal bowel disease have a 25-hydroxy vitamin D deficiency [13]. Finally, we can exclude that low 25-hydroxy-vitamin D levels may depend on the lack of activation of precursors since oral intake of vitamin D in patients with CIPO increases its serum levels [4].

On the other hand, low levels of 25-hydroxy-vitamin D may cause multiple negative effects as vitamin D performs multiple functions by binding its intracellular receptor and, subsequently, transcribing relevant genes [14,15]. Vitamin D regulates the absorption of calcium, which is involved in the intestinal motor activity [16], modulates the inflammatory response preventing cytokine storming, supports both innate and acquired immunity promoting antibacterial and antiviral defenses, and inhibits autoimmune response [17–22]. Furthermore, this fat-soluble vitamin affects the gut homeostasis interacting with the microbiome through the stimulation of synthesis of intestinal antimicrobial peptides (i.e. cathelcidin, β-defensin, angiogenin-4) [23,24], contrasting dysbiosis, infections and the leaky gut. Overall, vitamin D reduces the inflammatory response, inhibiting the phenomena of autoimmunity [25], but also stimulates intestinal motility through the control of calcium level [26].

Ahmadzai *et al*. [27] reported that enteric glial type I lysophosphatidic acid receptors (LPAR1) closely correlated with normal intestinal motility. The expression of glial LPAR1 in the colon and ileum seems to be reduced in patients with CIPO, suggesting that enteric glial LPAR1 signaling regulates the gastrointestinal motility through the enteric glia and could contribute to the severe motility impairment in patients with CIPO. Alessio *et al*. [28] have shown that vitamin D deficiency significantly modifies the microglia, suggesting a possible role of these cells in the sensorial dysfunctions associated with hypovitaminosis D.

This study has some limitations. The most important limitation is the small sample size. However, CIPO is a rare disease, therefore limiting the possibility to perform a powerful study including a large sample of patients. In addition, a selection bias is very likely to occur and this may have affected our results. For example, the inclusion of patients with more severe disease due to the tertiary care setting of our center may explain why all patients with CIPO had vitamin D deficiency.

Currently, it is unclear whether higher serum vitamin D levels or high-dose personalized administration can prevent CIPO or modify the course.

In conclusion, our study showed that idiopathic CIPO is strongly associated with low serum levels of 25-hydroxy-vitamin D. Vitamin D deficiency may negatively affect intestinal permeability and motility, gut microbiome and mucosal immunity, thus contributing to the severity of disease and risk of complications. Thus, our

finding would further support to test serum level of vitamin D in all patients with CIPO and supplement vitamin D until normal levels are reached [29,30].

Prospective randomized studies with a large sample size are needed to confirm our findings and provide additional information on the causal link between CIPO and 25-hydroxy-vitamin D deficiency.

Acknowledgements

Conceptualization: A.P. and R.M.Z.; Methodology: A.P.; Investigation: A.P. and R.M.Z.; Data curation: A.P. and R.M.Z.; Writing – original draft preparation: R.M.Z., A.P., L.H.E., and E.D.; Writing – review and editing: R.M.Z., A.P., L.H.E., E.D., and A.V. All authors have read the manuscript and approved the final version.

The data presented in this study is available on reasonable request to the corresponding author.

Conflicts of interest

There are no conflicts of interest.

References

1 Faulk DL, Anuras S, Christensen J. Chronic intestinal pseudoobstruction. *Gastroenterology* 1978; 74:922–931.
2 Downes TJ, Cheruvu MS, Karunaratne TB, De Giorgio R, Farmer AD. Pathophysiology, diagnosis, and management of chronic intestinal pseudo-obstruction. *J Clin Gastroenterol* 2018; 52:477–489.
3 Lauro A, De Giorgio R, Pinna AD. Advancement in the clinical management of intestinal pseudo-obstruction. *Expert Rev Gastroenterol Hepatol* 2015; 9:197–208.
4 Di Nardo G, Zenzeri L, Guarino M, Molfino A, Parisi P, Barbara G, *et al*. Pharmacological and nutritional therapy of children and adults with chronic intestinal pseudo-obstruction. *Expert Rev Gastroenterol Hepatol* 2023; 17:325–341.
5 Radocchia G, Neroni B, Marazzato M, Capuzzo E, Zuccari S, Pantanella F, *et al*. Chronic intestinal pseudo-obstruction: is there a connection with gut microbiota? *Microorganisms* 2021; 9:2549.
6 Ahmed S, Sharman T. Intestinal pseudo-obstruction. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2023. http://www.ncbi.nlm.nih.gov/books/NBK507885/. [Accessed: 5 March 2024]
7 Bianco F, Lattanzio G, Lorenzini L, Mazzoni M, Clavenzani P, Calzà L, *et al*. Enteric neuromyopathies: highlights on genetic mechanisms underlying chronic intestinal pseudo-obstruction. *Biomolecules* 2022; 12:1849.
8 Panarese A, Pesce F, Porcelli P, Riezzo G, Iacovazzi PA, *et al*. Chronic functional constipation is strongly linked to vitamin D deficiency. *World J Gastroenterol* 2019; 25:1729–1740.
9 Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. *BMJ* 2014; 348:g2035.
10 Diaconu AD, Ostafie I, Ceasovschih A, Șorodoc V, Lionte C, Ancuța C, *et al*. Role of Vitamin D in systemic sclerosis: a systematic literature review. *J Immunol Res* 2021; 2021:9782994.
11 Massironi S, Cavalcoli F, Zilli A, Del Gobbo A, Ciafardini C, Bernasconi S, *et al*. Relevance of vitamin D deficiency in patients with chronic autoimmune atrophic gastritis: a prospective study. *BMC Gastroenterol* 2018; 18:172.
12 Bishop E, Ismailova A, Dimeloe S, Hewison M, White JH. Vitamin D and immune regulation: antibacterial, antiviral, anti-inflammatory. *JBMR Plus* 2020; 5:e10405.
13 Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, *et al*. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019; 68:s1–s106.
14 Rosen CJ. Clinical practice. Vitamin D insufficiency. *N Engl J Med* 2011; 364:248–254.
15 Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. *Chem Biol* 2014; 21:319–329.
16 Fischer V, Haffner-Luntzer M, Amling M, Ignatius A. Calcium and vitamin D in bone fracture healing and post-traumatic bone turnover. *Eur Cell Mater* 2018; 35:365–385.
17 Liu D, Xiaoni M, Qiuyue T, Weijie C, Xin F, *et al*. Vitamin D and multiple health outcomes: an umbrella review of observational studies, randomized controlled trials, and mendelian randomization studies. *Adv Nutr* 2022; 13:1044–1062.
18 Hussein HM, Elyamany MF, Rashed LA, Sallam NA. Vitamin D mitigates diabetes-associated metabolic and cognitive dysfunction by modulating gut microbiota and colonic cannabinoid receptor 1. *Eur J Pharm Sci* 2022; 170:106105.
19 Bizzaro G, Antico A, Fortunato A, Bizzaro N. Vitamin D and autoimmune diseases: is vitamin D receptor (VDR) polymorphism the culprit? *Isr Med Assoc J* 2017; 19:438–443.
20 Ganz J, Ratcliffe EM. Who's talking to whom: microbiome-enteric nervous system interactions in early life. *Am J Physiol Gastrointest Liver Physiol* 2023; 324:G196–G206.
21 Rolig AS, Mittge EK, Ganz J, Troll JV, Melancon E, Wiles TJ, *et al*. The enteric nervous system promotes intestinal health by constraining microbiota composition. *PLoS Biol* 2017; 15:e2000689.
22 Foong JPP, Hung LY, Poon S, Savidge TC, Bornstein JC. Early life interaction between the microbiota and the enteric nervous system. *Am J Physiol Gastrointest Liver Physiol* 2020; 319:G541–G548.
23 Calder PC, Ortega EF, Meydani SN, Adkins Y, Stephensen CB, Thompson B, *et al*. Nutrition, immunosenescence, and infectious disease: an overview of the scientific evidence on micronutrients and on modulation of the gut microbiota. *Adv Nutr* 2022; 13:S1–S26.
24 Koduah P, Paul F, Dörr JM. Vitamin D in the prevention, prediction and treatment of neurodegenerative and neuroinflammatory diseases. *EPMA J* 2017; 8:313–325.
25 Cui P, Lu W, Wang J, Wang F, Zhang X, Hou X, *et al*. Microglia/macrophages require vitamin D signaling to restrain neuroinflammation and brain injury in a murine ischemic stroke model. *J Neuroinflammation* 2023; 20:63.
26 Gracia-Marco L. Calcium, vitamin D, and health. *Nutrients* 2020; 12:416.
27 Ahmadzai MM, McClain JL, Dharshika C, Seguella L, Giancola F, De Giorgio R, *et al*. LPAR1 regulates enteric nervous system function through glial signaling and contributes to chronic intestinal pseudo-obstruction. *J Clin Invest* 2022; 132:e149464.
28 Alessio N, Belardo C, Trotta MC, Paino S, Boccella S, Gargano F, *et al*. Vitamin D deficiency induces chronic pain and microglial phenotypic changes in mice. *Int J Mol Sci* 2021; 22:3604.
29 Alshahrani F, Aljohani N. Vitamin D: deficiency, sufficiency and toxicity. *Nutrients* 2013; 5:3605–3616.
30 Vieth R. Vitamin D supplementation: cholecalciferol, calcifediol, and calcitriol. *Eur J Clin Nutr* 2020; 74:1493–1497.