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Increased serum 1,25-dihydroxyvitamin D levels in gynecologic cancer patients with Post-Acute-Covid-Sequela (PASC)/Long COVID

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ABSTRACT

Post-acute sequelae of COVID-19 (PASC), also known as Long-Covid (LC), may affect 10–30 % of COVID-infected patients, and is characterized by a variety of debilitating symptoms lasting over 3 months after the acute infection, including but not limited to dyspnea, fatigue, and musculoskeletal, cognitive, and/or mental health impairments. Vitamin D is an essential nutrient primarily recognized for its role in regulating calcium and bone health but also endowed with potent anti-inflammatory activity affecting a variety of immune cells. We retrospectively evaluated the plasmatic levels of both 1,25-dihydroxyvitamin-D (1,25 OH), and 25-hydroxyvitamin-D (25 OH), the active and storage forms of vitamin-D3, respectively, in the serum of gynecologic cancer patients affected by PASC/LC vs control cancer patients. We found elevated 1,25-dihydroxyvitamin-D levels in 5 out of 5 of the PASC/LC patients (mean ± SD = 97.2 ± 26.9 pg/mL) versus 0 out of 10 of randomly selected cancer control patients (44.9 ± 17.2 pg/mL, p = 0.0005). In contrast, no significant difference was noted in the levels of 25-dihydroxyvitamin-D in PASC/LC (mean ± SD = 48.2 ± 15.8 ng/mL) versus controls (43.0 ± 11.6 ng/mL, p = 0.48). Importantly, abnormal levels of vitamin D were found to persist for at least 2 years in patients with long covid symptoms. The active form (1,25OH) but not the storage form (25 OH) of vitamin-D is significantly elevated in PASC/LC cancer patients. Abnormally and persistently elevated 1,25OH levels, similarly to sarcoidosis patients, may represent the results of extrarenal conversion of vitamin D by activated macrophages, and a novel biomarker of persistent inflammation in gynecologic cancer patients with PASC/LC.

1. Introduction

Up to 30 % of recovering COVID-19 patients including asymptomatic and mild/moderate cases may develop persistent debilitating symptoms, including but not limited to shortness of breath (SOB), decreased exercise tolerance, brain fog, cognitive dysfunction, fatigue, chest pain, chronic pain, palpitations, and gastrointestinal symptoms (Ceban et al., 2022; Soriano et al., 2022). While there is limited data available on PASC/LC in cancer patients and how it may affect their cancer progression, care, and treatment, recent reports suggest that up to 60 % of cancer patients diagnosed with COVID-19 and followed up for a up to 14 months may develop PASC/LC (Dagher et al., 2023; Cortellini, et al., 2023). Importantly, in some of these studies, female cancer patients were more likely than male patients to report persistence of PASC/LC symptoms (Dagher et al., 2023).

Vitamin D is an essential nutrient that plays a crucial role in maintaining bone integrity, immune function, and overall health (Bikle, 2014). Adequate levels of vitamin D are important for proper calcium absorption, regulation of gene expression in a multitude of body cells, and modulation of immune responses (Bikle, 2014). Vitamin D exists in different forms, with the most biologically active form being 1,25-dihydroxyvitamin D (1,25 OH) vitamin (calcitriol). The process of converting vitamin D from its inactive forms to its active form involves several steps. The first one is the synthesis of vitamin D in the skin from 7-dehydrocholesterol upon exposure to UVB radiation. This form of vitamin D, known as cholecalciferol, has a very short half-life of approximately 1–2 days in the blood. Cholecalciferol is then transported to the liver, where it is converted to 25-hydroxy (25 OH) vitamin D (calcifediol). Calcifediol has a longer half-life of approximately 2–3 weeks in the blood, making it a more reliable indicator of vitamin D status (Bikle, 2014). From the liver, calcifediol is transported to the kidneys, where it is converted to calcitriol (1,25-dihydroxyvitamin D), the biologically active form of vitamin D. Calcitriol has a half-life of approximately 4–6 h in the blood, but it is highly potent and can interact with vitamin D receptors (VDRs)

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throughout the body (Bikle, 2014). VDRs are found in many different tissues and cell types, including but not limited to bone, muscle, intestinal cells, and on a variety of immune cells including lymphocytes, macrophages, dendritic and mast cells (Bikle, 2014; Wang et al., 2012).

Under normal, homeostatic body conditions, 25-hydroxy (25-OH) vitamin D (calcifediol) is converted to calcitriol (1,25-dihydroxyvitamin D) in the cells of the kidneys (Bikle, 2014). During pregnancy or pathologic/inflammatory conditions, however, other human cells known to express 1α-hydroxylase (Cyp27B1), the enzyme responsible for the final and rate-limiting step in the synthesis of the active 1,25-dihydroxyvitamin D3 (1,25D3), may also contribute to the conversion of 25-hydroxy (25 OH) into 1,25(OH)2D3 (Adams et al., 1983; Barbour et al., 1981; Evans et al., 2006; Inui et al., 2001; Mason et al., 1984; Zehnder et al., 2002; Wang et al., 2012). Consistent with this view, cultures of pulmonary alveolar macrophages and/or sarcoid lymph-node homogenates have provided strong experimental evidence to demonstrate the capability of inflamed macrophages to support the extrarenal conversion of 25(OH)D to 1,25-dihydroxyvitamin D in sarcoidosis patients (Adams et al., 1983; Mason et al., 1984; Inui et al., 2001). These studies, combined with clinical reports demonstrating hypercalcemia in anephric patients with sarcoidosis (Barbour et al., 1981) were paramount in unraveling the immunomodulatory role of 1,25-dihydroxyvitamin D in granulomatous diseases such as sarcoidosis and tuberculosis as well as unequivocally demonstrating extrarenal production of 1,25-dihydroxyvitamin D by activated/inflamed human macrophages.

In this retrospective study, we report to our knowledge for the first time, a significant and persistent increase in the serum levels of the active form of vitamin D (ie, 1,25-dihydroxyvitamin D) in a handful of PASC/LC cancer patients followed in our clinic and with storage and active form of vitamin D3 blood measurements available. Importantly, none of the randomly selected gynecologic cancer control patients without PASC/LC symptoms demonstrated elevation in 1,25-dihydroxyvitamin D. Abnormally and persistently elevated 1,25-dihydroxyvitamin D levels in cancer patients with PASC/LC, similarly to sarcoidosis patients with active disease, may represent the results of extrarenal conversion of vitamin D by activated macrophages, and a novel biomarker for PASC/LC patients.

2. Cases

We retrospectively evaluated the plasmatic levels of both 1,25-dihydroxyvitamin D ($1,25(OH)_2$-D3), the active form of the vitamin, and 25-hydroxyvitamin D (ie, 25(OH)-D3), the storage form of the vitamin, in gynecologic patients affected by PASC/LC symptoms (ie, 3 with a history of gynecologic tumors and 2 with a history of endometritis or complex ovarian cysts) followed in our clinic. We compared their levels to those detected in 10 randomly selected gynecologic cancer patients without PASC/LC symptoms using 2-sided two-sample t-tests at $P < 0.05$ significance level. We also considered $1,25(OH)_2$-D3 levels to be elevated if they exceeded Quest Laboratory's reference range of 18–72 pg/mL. The characteristics of the PASC/LC and control cancer patients are described in Table 1. We found elevated levels of 1,25-dihydroxyvitamin D in 5 out of 5 of the PASC/LC patients (mean ± SD = 97.2 ± 26.9 pg/mL) versus 0 out of 10 of randomly selected control patients (44.9 ± 17.2 pg/mL, p = 0.0005)(Fig. 1). In contrast, no significant difference was noted in the levels of the 25-hydroxyvitamin D in PASC/LC (mean ± SD = 48.2 ± 15.8 ng/mL) vs controls (43.0 ± 11.6 ng/mL, p = 0.48)(Fig. 1). As representatively demonstrated in Fig. 2 for PASC/LC patients where multiple longitudinal vitamin D 1,25OH and 25OH blood collections were available, prolonged abnormalities in the levels of the active form of vitamin D were noted. Importantly, both these PASC/LC cancer patients reported long lasting (ie, over 2 years) debilitating symptoms (ie, shortness of breath (SOB), fatigue, etc.) since the onset of the acute covid infection.

3. Discussion

Several studies have reported that cancer patients, due to their clinical challenges in cancer management, including aging, immunosuppression, and chronic comorbidities may be more susceptible to SARS-CoV-2 infection and are at a higher risk of severe COVID-19 than the general population (Yuan et al., 2020). Consistent with this higher vulnerability, recent data have suggested that cancer patients may be more susceptible to develop long-lasting debilitating symptoms including but not limited to shortness of breath (SOB), decreased exercise tolerance, brain fog, cognitive dysfunction, fatigue, dysautonomia including postural orthostatic tachycardia (POTS), chest pain and chronic pain, palpitations, and gastrointestinal symptoms after the acute infection, with up to 60 % developing PASC/LC (Dagher et al., 2023; Cortellini, et al., 2023).

The pathophysiologic mechanisms underlying the post-COVID prolonged and disabling symptoms remain poorly understood. However, several studies have provided strong experimental evidence to suggest that viral persistence triggering prolonged organs' inflammation might be responsible for at least some of the PASC/LC symptoms. Indeed, multiple authors have reported the presence of viral RNA or viral antigens in the human olfactory epithelium, lung cells, blood, feces and gastrointestinal tissues months after the initial diagnosis of COVID-19 (de Melo et al., 2021; Bussani et al., 2020; Craddock et al., 2023; Zollner et al., 2022). Importantly, a significant number of non-classical monocytes was found to contain/transport SARS-CoV-2 S1 protein in PASC/LC patients up to 15 months post-infection (Patterson et al., 2022; Cheung et al., 2022). Consistent with these data, SARS-CoV-2 infection has been demonstrated to leave an inflammatory imprint in the monocyte/macrophage compartment that drives aberrant macrophage effector functions and metabolism, resulting in long-term immune aberrations lasting for months even in patients recovering from mild COVID-19 (Patterson et al., 2022; Schultheiß et al., 2023). Taken

Table 1

Number	Age	Race	Gyn Pathology	Date of first COVID infection	Vitamin D3 supplement	Long COVID Symptoms
1	73	black	endometrial cancer	n/a	yes	no
2	64	white	endometrial cancer	n/a	yes	no
3	85	black	endometrial cancer	1/2/2020	no	no
4	63	white	ovarian cancer	10/9/2022	yes	no
5	63	white	cervical dysplasia	n/a	no	no
6	63	white	ovarian cancer	4/17/2020	yes	no
7	75	white	endometrial cancer	n/a	no	no
8	77	white	ovarian cancer	12/16/2022	yes	no
9	58	white	cervical cancer	n/a	no	no
10	69	black	endometrial cancer	1/21/2021	yes	no
11	65	white	endometrial cancer	4/20/2020	yes	yes
12	69	white	ovarian cancer	7/7/2020	yes	yes
13	70	white	endometrial cancer	7/9/2020	yes	yes
14	71	white	complex ovarian cyst	12/9/2022	no	yes
15	33	white	endometritis	3/26/2020	no	yes

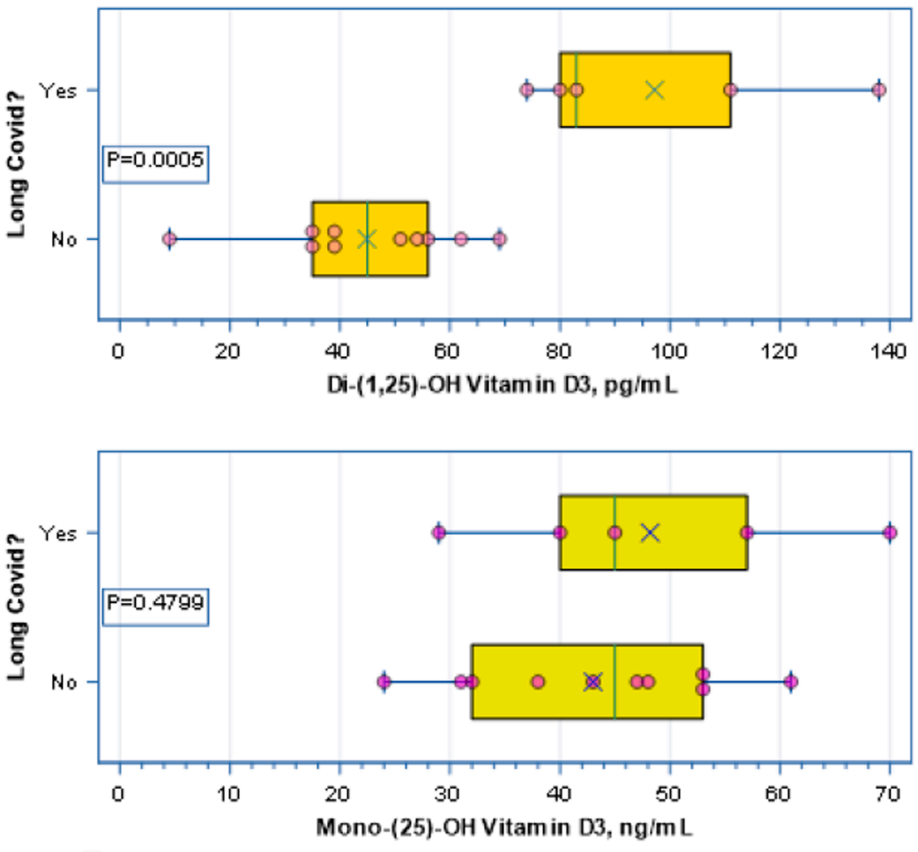

Fig. 1. Levels of vitamin D 25OH (left panel) and 1,25OH* (right panel) in 5 PASC/LC cancer patients vs 10 cancer controls. *Assays used: Vitamin D 1,25-Dihydroxy: YALE SCHOOL OF MEDICINE LABORATORY (reference range 25——66 pg/mL); QUEST LABORATORY (reference range 18——72 pg/mL).

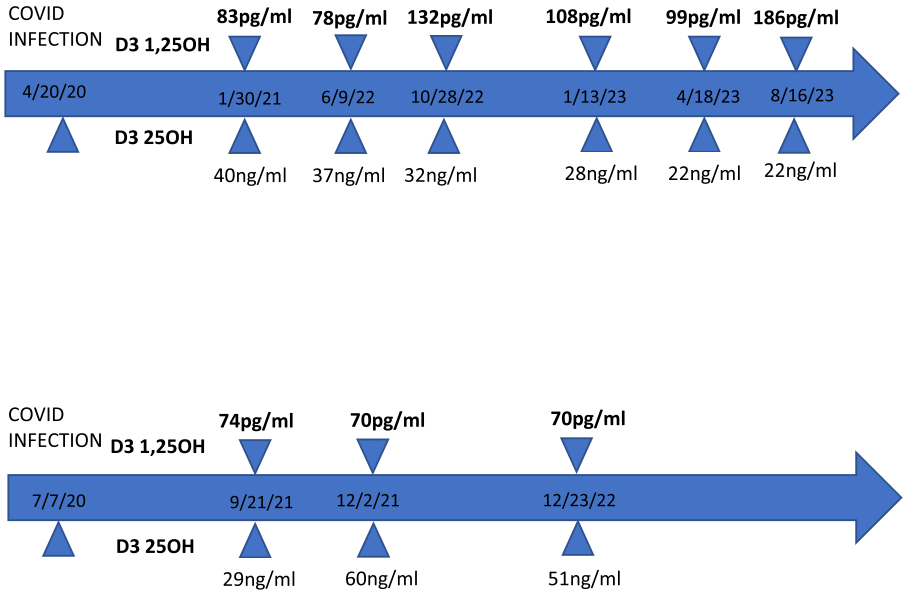

Fig. 2. Longitudinal Vitamin D3 25OH and 1,25OH serum values in two representative PASC/LC cancer patients (upper panel patient 11, lower panel patient 12) with multiple blood collection available over 2 years. *Values reported in bold are above normal range reference for the assays used.

together, these studies suggest that multiple tissues and organs including subpopulations of inflammatory cells such as monocyte/macrophages, dendritic cells and mast cells (Martens et al., 2020), may represent not only a potential COVID-19 viral antigen reservoir but also a persistent source of inflammation in at least a subset of PASC/LC patients.

The active form of vitamin D, 1,25-dihydroxyvitamin D3 (1,25 $(OH)_2$-D3) is endowed with multiple biological actions that extend far beyond its established effects on calcium homeostasis and bone metabolism (Bikle, 2014; Amon et al., 2022; Yang et al., 2013). Consistent with this view, 1,25$(OH)_2$-D3 has been shown to act as a potent

modulator of both innate and acquired immune responses, including: enhanced macrophage bacterial killing; suppression of natural killer (NK) cell function and mast cell degranulation/activation; inhibition of dendritic cell (DC) maturation; inhibition of T-cell proliferation; and modulation of T-cell phenotype to mention just a few [for review see (Martens et al., 2020; Amon et al., 2022)]. These and other observations have supported therapeutic applications for $1,25(OH)_2$-D3 in the treatment of autoimmune disease (Yang et al., 2013), and more recently, during COVID-19 infection [for review see (Argano et al., 2023)].

In our retrospective analysis we found levels of the active form of vitamin D (ie, 1,25-dihydroxyvitamin D) to be significantly elevated in gynecologic cancer patients affected by PASC/LC symptoms vs controls. In contrast, no significant differences were detected in the plasmatic levels of the storage form of vitamin D (ie, 25-hydroxyvitamin D). Macrophages, dendritic cells (DC), and mast cells (MC) residing in the peripheral tissues are known to express the enzyme 25-hydroxyvitamin D-1a-hydroxylase (CYP27B1) that catalyzes synthesis of 1,25(OH)2D3 from its inactive precursor, the major circulating form of vitamin D, 25-hydroxyvitamin D3 (25OHD3) (Cheung et al., 2022; Patterson et al., 2022; Schultheiß et al., 2023). Because of this fact, we are tempted to speculate that, similarly to patients with active sarcoidosis (Adams et al., 1983; Mason et al., 1984; Inui et al., 2001; Barbour et al., 1981), chronic activation of macrophages/DC caused by persistence of viral RNA or viral antigens (Bussani et al., 2020; Cheung et al., 2022; Craddock et al., 2023; de Melo et al., 2021; Schultheiß et al., 2023; Zollner et al., 2022) might trigger prolonged tissue inflammation and cause extrarenal hydroxylation of vitamin D3 in PASC/LC patients. Indeed, since many cells within the immune system express the nuclear receptor for $1,25(OH)_2$-D3 (vitamin D receptor [VDR]) and are sensitive to vitamin D, high extrarenal production of the active form of vitamin D by resident macrophages/DC may act as an autocrine/paracrine regulator of immune responses in the tissues of PASC/LC patients (Martens et al., 2020; Amon et al., 2022; Yang et al., 2013). Importantly, in our small series, abnormalities in the levels of the active form of vitamin D were found to persist for at least 2 years in gynecologic cancer patients with prolonged long COVID symptoms. Taken together, these data suggest that chronic inflammation likely secondary to persistent viral antigen infection may cause extrarenal vitamin D hydroxylation and this abnormal status may persist for years in at least of subset of PASC patients. These findings are consistent with a recent report on a large number of PASC/LC patients demonstrating that their significant activity limitations did not significantly change over time (Ford et al., 2023).

In conclusion, we report that the active form ($1,25(OH)_2$) but not the storage form (25 OH) of vitamin D is significantly elevated in a subset of PASC/LC patients and that this status is likely the result of persistence inflammation caused by residual viral RNA or viral antigens. Abnormally and persistently elevated $1,25(OH)_2$-D3 levels in gynecologic cancer patients with PASC/LC, similarly to sarcoidosis patients with active disease, may represent the results of extrarenal conversion of vitamin D by activated macrophages/DC, and a novel biomarker of persistent tissue inflammation in PASC/LC patients.

Consent.

The retrospective chart review was approved by the Yale Human Research Protection Program, Institutional Review Boards, IRB Protocol ID: 2000030512.

Conflict of interest.

ADS reports grants from VERASTEM, PUMA, GILEAD, SYNTHON, MERCK, BOEHINGER-INGELHEIM, GENENTECH, and personal fees for consulting services from TESARO, EISAI, GSK, MERCK, and GILEAD. The other authors declare no conflict of interest.

Author contributions.

Stefania Bellone, Eric Siegel, and Alessandro D. Santin participated in drafting and revising this manuscript. All authors read and approved this manuscript to be submitted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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