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Review

Vitamin D and Primary Ciliary Dyskinesia: A Topic to Be Further Explored

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Abstract: Primary ciliary dyskinesia (PCD) is a genetic disease characterized by abnormalities in ciliary structure/function. The diagnosis of PCD relies on a combination of clinical evaluation and ultrastructural (electron microscopic) analysis of the ciliary architecture. This diagnosis may be challenging due to clinical and genetic heterogeneity and artifacts during the ciliary ultrastructure preparation and assessment. Recently, vitamin D supplementation has been proposed for several groups probably suffering from D-hypovitaminosis. Some patients with inflammatory bowel disease may have significant malabsorption, and vitamin D supplementation in these patients is recommended. Two recent reports suggest that a low plasmatic level of this vitamin is present in the PCD population. The utility of vitamin D supplementation may be essential in this group of individuals, and further investigations are warranted. Still, in examining the literature papers, it seems relevant that the authors concentrate solely on lung function in both studies. Future studies should probably target the intestinal function in patients with PCD independently from the vitamin D supplementation to fully evaluate its role.

Keywords: vitamin D; supplementation; diet; primary ciliary dyskinesia; quality; health care

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1. Introduction

Flagella and motile cilia show a conserved axonemal structure. They consist of a ring of nine microtubular doublets associated with a central pair of microtubules [1–4].

This architecture gives the classical 9 + 2 microtubular arrangement often searched for in patients harboring a cilia's potential defect (Figure 1). In examining the ciliary ultrastructure, the diagram of a transverse section of a normal cilium depicts the internal ultrastructure and the ciliary axis used to identify cilia orientation concerning each other. A ciliary membrane typically surrounds the axoneme (central core). It has nine peripheral microtubule doublets and two single central microtubules (Figure 1). The ultrastructural analysis is, however, challenging and needs to be carried out in several sections. Often some parts may be in focus.

In contrast, other details of the ultrastructural investigation may show the limitations of this technique on getting focused images in all fields (Figure 2).

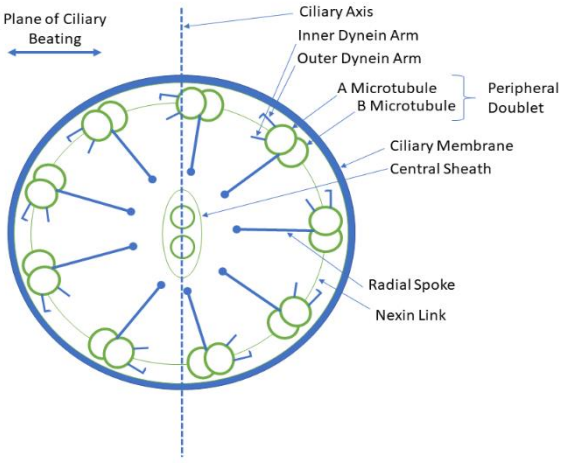

Figure 1. Ciliary Ultrastructu-re. A transverse section of a normal cilium is depicted in this diagram showing the internal ultrastructure and the ciliary axis used to identify cilia orientation with respect to each other. The central core or axoneme is surrounded by a ciliary membrane and has nine peripheral microtubule dou-blets associated with two single central microtubules.

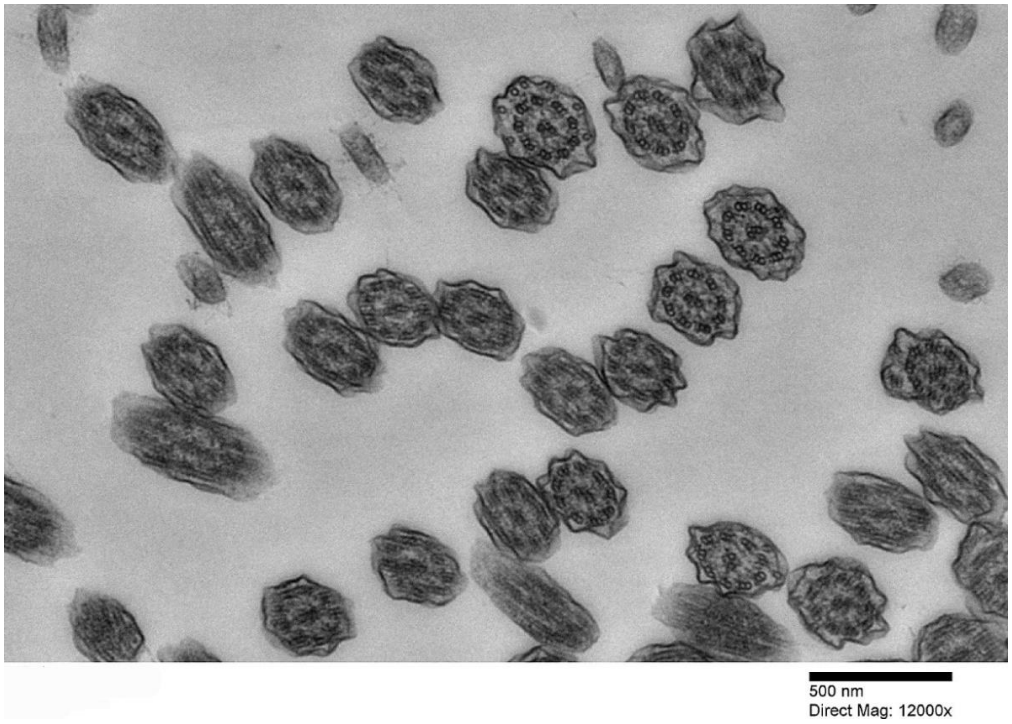

Figure 2. Cilia of a healthy individual showing a classic arrangement (transmission electron microscopy, see the bar for details regarding magnification). Some of these tangential sections were cut midway between the cell surface and the top of the waves. Ciliary cross-sections represent cilia in wave crests. Some cross-sections are not in focus because of the specific cut occurring at the time of the ciliary stroke. This is due to the technical difficulty in having all cross-sections with the same planar cut section.

There is a bridge-like structure interconnecting the central pair of microtubules C1 and C2. The bridge-like design and the central pair of microtubules constitute the main sheath or central pair complex (CPC). The composition of each outer doublet is critical, and there are type A and B microtubules connected by radial spokes (RS) to the CPC. The motility relies on the inner dynein arm's interaction (IDA) and outer dynein arm (ODA). They

are carried by the A-type tubule and develop toward the B-microtubule of the adjacent doublet. IDA and ODA form part of a specific protein complex of 96 nm repeat unit. It includes four identical ODAs, six single-headed IDAs, one two-headed IDA, the three Rs, and a single nexin–dynein regulatory complex (N-DRC). The activity of the dynein arms is regulated and coordinated by the N-DRC. In the sperm flagellum, which has an ultrastructurally similar axonemal structure, accessory structures are also recognized. They include the mitochondrial sheath (MS), fibrous sheath (FS), and outer dense fibers (ODFs) [4]. This anatomy is specific to the sperm tail. They are needed for fertile sperm production and critical for the movement of the sperm in the female reproductive tract. Their central doublet must orientate neighboring cilia to beat in a coordinated way in a parallel fashion. Such ciliary beating coordination may be assessed by measuring the standard deviation of the angles formed between the central microtubules of neighboring cilia with the x-axis [5,6].

Motile cilia malfunction causes primary ciliary dyskinesia or PCD. It is a genetic disease, which affects nearly 1:10,000 people worldwide with slightly geographic variation [7]. The symptomatology begins in the newborn period. The spectrum includes a chronic nasal discharge associated with a wet cough. In childhood, it progresses to recurrent upper and lower respiratory infections. It may eventually evolve in pulmonary scarring with the formation of bronchiectasis. It is well known that a dysfunction of the airways' motile cilia is the basis of the symptoms. The airway motile cilia are specifically accountable for mucus clearance in the airways. In addition, motile cilia are crucial for the life of an organism. They are present in the brain, fallopian tube, eustachian tube, and middle ear. They function in fluid movement and play a crucial role in the embryonic node during development. *Situs inversus*, opposite of the *situs solitus* with a typical arrangement, is a congenital condition in which the major visceral organs are mirrored or reversed from their standard locations [8–10]. In approximately half of the patients harboring PCD, there are defects in the nodal cilia, which cause *situs inversus* [8,11,12]. PCD had some very well know eponyms and synonyms, including "Kartagener Syndrome" (bronchiectasis, chronic sinusitis, and *situs inversus totalis*) and "Immotile Cilia Syndrome" (after detection of immotile respiratory cilia and immotile sperm in subjects with Kartagener Syndrome) [13]. The different mutations cause different ciliary phenotypes, which also impact the clinical features of the disease. For example, a mutation that affects some components of the ODAs and IDAs may result in immotile cilia mutation that affects the radial spoke proteins resulting in cilia with circular motions. On the other side, mutations that affect *CCDC39* and *CCDC40* genes (Coiled-Coil Domain Containing proteins 39 and 40) induce a more severe clinical phenotype. The Coiled-Coil Domain-Containing Protein 114 gene (*CCDC114*) is associated with the biogenesis of cilia. It is crucial for the attachment of the outer dynein arms (ODAs) to the axoneme of cilia. Recently, mutations in the *CCDC114* gene have been identified in a subtype of PCD named ciliary dyskinesia 20 (CILD20) [14–18]. In 78 patients with PCD, Noone et al. investigated 76 patients using ciliary ultrastructural analysis [19]. The multiple PCD phenotypes included four major categories of structural ciliary defects. They are (1) outer dynein arm (ODA) alone, (2) inner dynein arm (IDA) alone, (3) defects in both outer and inner dynein arms, and (4) central apparatus defects. This last category is typically subdivided into defects of the central pair, radial spokes, or nexin links. They found defects in ODA alone, IDA alone, ODA and IDA combined, and central apparatus in 43%, 29%, 24%, and 4%, respectively [19]. Although heavily debated due to reproducibility issues in a clinical setting, the central doublet orientation deviations of over 20 degrees from each other may indicate the cilia's failure to move in a coordinated wave-like fashion [5,6,20–23].

Although the ultrastructural analysis of cilia is quite well established worldwide, this assay has limited detection sensitivity. Not all PCD mutations cause cilia defects visualized by electron microscopy. The method is subject to artifacts due to numerous technical biases [9,24]. The functional analysis represents another critical approach toward our current understanding of ciliary motility. Still, this investigation remains technically

challenging, and the relationship between ciliary motion and mucus transport has not been well characterized. The lifelong burden of PCD to pediatric patients changes probably slightly when they become adults. The focus moves on bronchiectasis, and the otologic disturbances become quite attenuated. However, the burden can be focused on fertility issues, mainly when the couple is attempting to have a child. Despite the extensive and increasing understanding of the spectrum of cilia structural defects in PCD, only a few reports concentrate on vitamin D's role in PCD. The scope of this narrative review is attempting to fill this gap in the medical literature.

2. PCD under the Lens

PCD is characterized by genetic heterogeneity with variable clinical impact. Genetic studies have discovered 40 PCD-associated genes. Mutations in known PCD genes are responsible for nearly 70% of all PCD cases [13]. Predictably, more PCD genes will be found in this decade. There is an increasing awareness of this condition, and genetic sequencing has reached optimal levels. In tertiary centers, more patients with clinical phenotypes suggestive of PCD are often evaluated. The classic "hallmark" of PCD relies on the ultrastructural axonemal defects, including an absence of inner and outer dynein arms, absence of the outer dynein arm only, lack of inner dynein arms associated with microtubular disorganization, and/or central pair organization defects (Figure 3) [25].

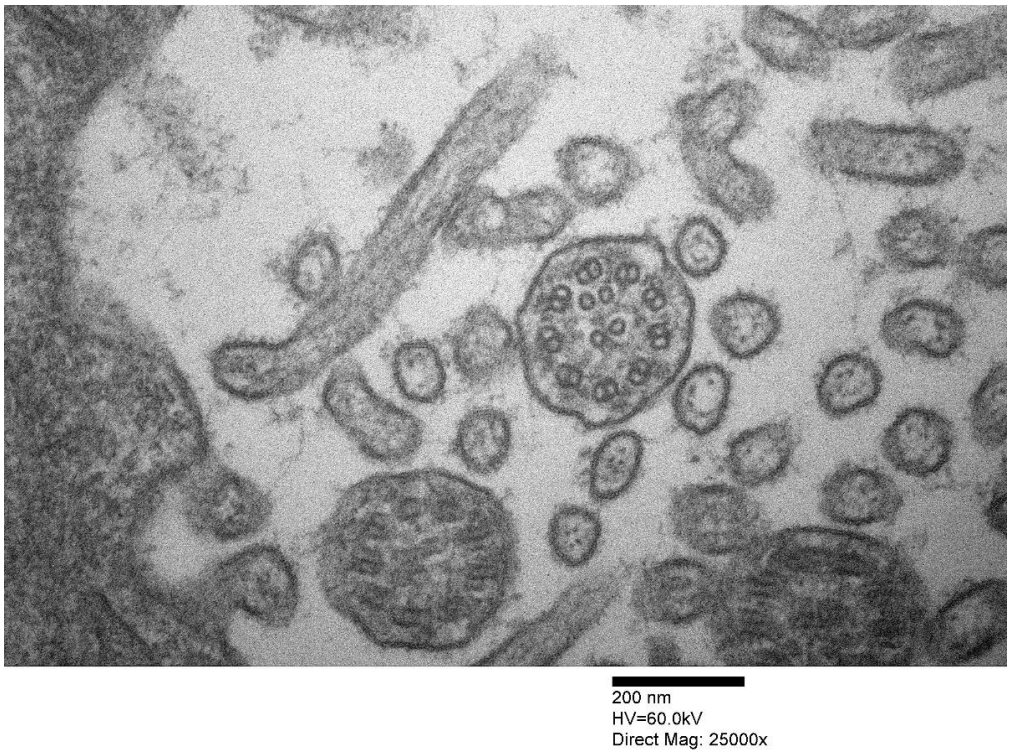

Figure 3. Cilia of a patient with primary ciliary dyskinesia showing microtubular disorganization (transmission electron microscopy, see the bar for details regarding magnification).

It has been projected that approximately one-third of genetically proven PCD cases have standard or normal-appearing ciliary axonemal structure. In addition to artifacts and suboptimal expertise in some morphologists, this data emphasizes electron microscopy limitations to detect subtle changes in structure. Although the transmission electron microscopy (TEM) is still key for the diagnosis with the analysis of the respiratory epithelium by nasal brushing for identification of ciliary structural defects, there are also more tests for making a diagnosis of PCD under all circumstances. The clinical history (neonatal respiratory distress, body laterality defects) should be accompanied by a series of tests that can be used to confirm the diagnosis. Nasal nitric oxide gas is decreased in most patients

with PCD. In addition, defects of the ciliary beat pattern and frequency can be identified by high-speed video microscopy analysis (HSVMA) [26]. HSVMA harbors tremendous rates of sensitivity and specificity for PCD. In particular, specific beat patterns have been linked to specific ultrastructural defects. The analysis should also include immunofluorescence to look at cilia protein defects, which can be associated to more specialized TEM. The identification of numerous genes coding for proteins, which have a prominent role in motile cilia structure, formation, and function, has placed this technique in the forefront in most tertiary centers dealing with PCD patients. Moreover, gene panels have currently been proposed in numerous centers independently from the genetic heterogeneity [4].

3. Vitamin D

The "English Disease" or rickets, scurvy, and beriberi are known to have accompanied human civilization for centuries in both old and new continents [27–29]. Rickets is no longer considered the disease relegated to history or limited to low-income countries. Although not uniformly accepted, some reviews and clinical studies have pinpointed the low vitamin D level in patients affected by COVID-19 [30–33]. This aspect has brought significant attention to this component's crucial role in our diet [28]. Up to the end of the 1990s there was not much interest in nutritional rickets. After the turn of the century, there was a resurgence of interest in rickets and vitamin D status. The number of original reports and systematic reviews of patients and diseases associated with vitamin D deficiency was vastly increasing. Numerous clinical laboratories are being asked to measure the circulating 25-hydroxy(OH)-vitamin D (25[OH]D) levels in both pediatric and adult patients [34–38]. In addition, vitamin D may have a crucial role in bone osteoporosis, which may be essential in migrants and individuals with HIV infection [39–43]. Child neglect cases discovered in forensic practice and unpublished cases debated only in courts may represent the tip of an iceberg [29,44]. Of note, extensive population surveys, such as the Nutrition Examination Survey and National Health, suggest that important sectors of infant and childhood and pregnant women populations are or will be affected by vitamin D inadequacy (at some point) in their life [45–50]. The change of the habits with indoor living, less sunlight exposure, dietary choices, and increasing rates of dietary allergy are likely playing a significant role in the increase of this rate in some segments of the worldwide population, according to the most recent evaluation of public health indicators [48,51–59].

Vitamin D is a fat-soluble vitamin. It has a unique metabolic pathway. It is predominantly made in the skin during sunlight exposure, unlike vitamins A, E, and K. These three vitamins are rigorously absorbed from the diet. Indoor living is a significant drawback to our civilization. Conventionally, vitamin D plays a leading role in calcium homeostasis. Vitamin D deficiency is an essential cause of rickets, osteomalacia, and osteoporosis in the human population [60–63]. The most recent immunologic evidence indicates that vitamin D is tightly linked to immunity, inflammation, and cancer pathways [64–66]. The immune system cellular components possess vitamin D receptors (VDRs). These receptors are capable of metabolizing the active form of vitamin D [calcitriol, 1,25-dihydroxy vitamin D, $1,25(OH)_2D$] [67–70]. The storage form of vitamin D is 25-hydroxyvitamin D or 25(OH)D. It can be converted by activated T and B cells to $1,25(OH)_2D$ in human cells in vitro [71]. There is a local activity of 1,25(OH)2D on immune cells with autocrine or paracrine fashion. This aspect is crucial in the infection, as suggested in COVID-19 infection, the coronavirus 2019 infection caused by the Severe Acute Respiratory Syndrome type II (SARS-CoV-2), despite controversial data [30–33].

Moreover, peripheral blood mononuclear cells (PBMC) harbor VDR providing support for vitamin D's significant role in regulating the immune system and infectious diseases [72]. Other than activity on immune cells, vitamin D increases the absorption of calcium from the small intestine. This aspect visibly showed that vitamin D is an essential factor in the utilization of dietary calcium. Nicolaysen et al. and Haavaldsen et al. also observed that animals on a low calcium diet had much greater calcium absorption efficiency than animals fed an adequate amount of calcium [73–75]. As identified that calmodulin is localized

in the hamster's ciliated cells, and the prominent role of calcium for cilia's bioenergetic activity, the connection with immunity is more robust [76–81].

Vitamin D is crucial in maintaining airway homeostasis and innate immunity [82–85]. Vitamin D is a potent fat-soluble vitamin essential for healthy bones and cell growth and immune function. Vitamin D is known for its role in the regulation of calcium homeostasis and bone metabolism. Still, multiple studies have shown that it also acts as an essential regulator of host defense and immunity, including respiratory host defense. Transforming growth factor-beta 1 (TGF-β1) reduces the host defense of airway epithelial cells by altering the vitamin D-mediated expression of host defense peptides and proteins [82]. When primary CD4+ T cells from healthy donors were cultured in Th17-polarizing conditions, vitamin D reduced the expression of Th17 markers and their secretion of proinflammatory cytokines. It entailed mainly interleukin 17A (IL-17A) and interferon-gamma (IFN-γ). It induced an expansion of CD4+ T cell subset expressing the highest levels of CD25 (termed $CD25^{hi}$) cells. It also upregulated their expression of CTLA-4 and Foxp3 regulatory markers [86]. In addition, the active form of vitamin D3 during CD8+ T-cell differentiation prevented IL-4–induced conversion to Tc2 IL-13 producers [83,86,87]. It seems that this may be particularly relevant for asthmatic children. Several studies have identified that low serum levels of vitamin D are associated with increased exacerbations, decreased lung function, increased airway inflammation, and, ultimately, poor prognosis in asthmatic patients [85]. Several studies, principally in children, suggest that vitamin D insufficiency is associated with asthma severity and more inadequate control [83]. Finally, there are two studies in healthy children where vitamin D's preventive administration lowered the respiratory infection risk [88,89]. Influenza A occurred in 10.8% of a group of 167 schoolchildren receiving 1200 IU/d vitamin D3. This data was significantly lower than the placebo group, where over 18.6% of children were infected. In healthy kids, Xiao et al. [90] found that only in the Urashima's study [88], where the risk of viral infection was lowered, was the vitamin D supplementation 1200 IU/d. However, vitamin D supplement plays a non-novel role in regulating lung microbiome and airway function. Still, it seems to positively affect patients suffering from inflammatory bowel disease by modulating the gut microbiome and increasing the abundance of beneficial bacterial strains [84]. The cause of the growth failure of patients with PCD may be multifactorial and is likely because of increased respiratory effort, possible effects of chronic inflammation, and suboptimal nutrition intake, although a duodenal biopsy is rarely part of the workup of PCD patients and to our knowledge, this has yet to be described. A comprehensive study between the University of Alberta, Edmonton, Alberta, Canada, the Department of Gastroenterology and Hepatology, Vrije Universiteit Medical Center, Amsterdam, and The Netherlands on potential abnormal duodenal histology in several categories with malabsorption was performed [91].

Vitamin D is a vital supplement to the human diet. Although most people are satisfactorily protected against vitamin D deficiency, others show a level of susceptibility to develop such deficiency, which may target several critical functions of the organism. The National Institutes for Health (NIH) recommends supplementation of this vitamin D for some categories. They include exclusively and partially breastfed infants, people living in colder climates and less sunlight exposure, housebound people, or individuals who work night shifts, harboring a body mass index (BMI) of 30 or over, who have undergone gastric bypass surgery, suffering from inflammatory bowel disease, or cover their skin for religious reasons. The infants should receive 400 international units (IU) (10 micrograms [mcg]) of vitamin D per day until weaning. The dosage for other age groups varies. Up to the 70th year of age, the dosage of vitamin D supplementation is 600 IU (15 mcg).

In contrast, individuals older than 70 years should receive 800 IU (20 mcg) of vitamin D. On the other hand, skin exposure for 5–30 min, with the face, arms, legs, or back exposed, may be enough for most individuals at least twice per week. However, underlying conditions may still require supplementation to be added.

4. Vitamin D Role in PCD

There is a positive association between lung function and body mass index in PCD [92,93], but the nutritional status of children affected with PCD may be relatively low. Marino et al. found that the healthy phenotype of a cohort of children with PCD may be quite altered [94]. Although weak, there is an association between lung function and nutritional status and the bioelectrical impedance spectroscopy (BIS) phase-angle measures. BIS has been explicitly utilized to determine body composition in different settings. It has been shown to identify differences in nutritional state and clinical outcome. Marino et al. emphasized that the use of BIS phase-angle may allow for early identification of at-risk children and may, therefore, be of benefit for nutritional assessments in the appropriate clinical setting [94]. A low BIS phase angle is associated with more inferior dietary status, which may precede anthropometric changes and impact clinical outcomes. Marino et al. found that in children with PCD, there were some associations between BIS phase angle, nutritional status, and clinical outcomes. They advocate for the routine use of BIS phase angle to add sensitivity and specificity in identifying children with nutritional risk earlier than using anthropometry alone. Marino et al.'s study [94] is paramount for identifying PCD patients at nutritional risk and looking for biomarkers of chronic inflammation in PCD. Their study involved 43 children, of which 51% were male. The average age at diagnosis was 2.7 $\pm$ 3.8 years, and at the time of the survey was 7.0 $\pm$ 3.6 years. Although none of the children studied had a low energy intake, 63% had excessive intake and 6% of children consumed inadequate amounts of protein, and 72% had a consumption of protein 200% of the reference nutrient intake (RNI) [95,96]. The authors found no associations between energy and protein intake concerning BMI, height for age, or BIS phase angle. Although there were no statistically significant variations between the groups, the FEV1 z score was higher in those with a protein intake of 200% of RNI than those with an adequate protein intake. Remarkably, vitamin D insufficiency (<50 nmol/L) was detected in 54% of the patients in the cohort where the plasma was available. Marino et al.'s study data are critical because children in their cohort had insufficient vitamin D levels, but all other micronutrient levels were within the normal range. The observation that lower nutritional status is associated with more impaired lung function in PCD patients, although weak, is similar to that seen in patients with cystic fibrosis (CF), with a relationship described between FEV1 and BMI. Although CF's main nutritional issues are probably due to intestinal malabsorption secondary to pancreatic insufficiency, PCD patients' data may be puzzling. This aspect may suggest that chronic suppurative lung disease, independently from pancreatic involvement, may negatively impact nutritional status [97]. This data may indicate that an abnormal ciliary function is associated with malabsorption but need to be explored further in future extensive studies. Marino et al.'s research findings are utmost. Still, limitations need to be considered, including dietary intake methods and a three-day semiquantitative food diary different from the seven-day diary. Apart from the suggested benefit of a multicenter design, the potentiality to evaluate a duodenal biopsy may be expected for complete identification of the normal intestinal anatomy [91].

Another study involved the measurement of vitamin D levels in 22 patients with PCD [98]. Mirra et al. [98] studied 15 males and seven females, 10.5 years (range, 2–34 years). These authors found that 72% of PCD patients were vitamin-D deficient-to-insufficient and 28% only were sufficient. In addition, 79% of PCD individuals had limitations in performing vigorous activities, and 53% completed less than 3 h of physical activity per week. Mirra et al.'s study data are also vital because they found hypovitaminosis D in young Italian individuals. The subjects attended the Department of Translational Medical Sciences, Federico II University, Naples, Italy, the reference center for PCD in Campania, Southern Italy. Patients lived in Naples metropolitan area (latitude, 40°49′ N; elevation, 17 m) and were evaluated from March through June 2012. These two aspects are fundamental because Naples is in Italy's Southern regions, and the observation was in the spring of the year. Thus, we would probably expect lower vitamin D levels in the northern areas of Italy or Europe and winter.

Another aspect, which has not been raised by the authors in their cross-sectional study, concerns the affected individuals' diet. In Campania, cheese and milk products are the mainstays of their diet. Thus, if we consider Mirra et al.'s findings and associated with the Marino's data, we should strongly suggest evaluating these individuals' duodenal function. Vitamin D plays a crucial part in improving the innate immune response [83]. Interestingly, there is some evidence that vitamin D is also valuable for the current pandemic of COVID-19, a multisystemic infection caused by SARS-CoV-2 [99–101]. These two studies reveal an extra-immunologic role of vitamin D, particularly the correct intestinal absorption. Vitamin D may play a considerable role in the growth and of individuals with PCD. Children in Western societies are, however, also at risk if living in high-risk groups. Dwyer et al. [102] studied records of preschool vegetarian children's dietary intake. They found that a macrobiotic vegetarian diet provides marginal amounts of vitamin D, calcium, and phosphorus. Children on macrobiotic diets show physical and roentgenographic findings indicative of nutritional rickets more often than in the case of other vegetarian diets. Dagnelie et al. also studied vitamin D metabolism in Caucasian 10–20-month-old infants on a macrobiotic and omnivorous diet. These authors found that low availability of the calcium mineral in the macrobiotic diet was an independent factor in causing the high prevalence of rickets in these infants [103]. The macrobiotic diet precludes milk products and incorporates a high fiber intake. Both factors may have adverse effects on bone development in young children. Occult rickets cases have been reported and represent a drama for Asian immigrant children in the United Kingdom and worldwide [104–111].

5. Conclusions

In this paper, we revised the PCD and considered the increasing role of hypovitaminosis D with this genetic disease. A caveat of this review is that very few previous investigations target the role of vitamin D in PCD disease, so it is difficult to make conclusions based on this review. The results from Mirra et al. and Marino et al. are insufficient to suggest a role of vitamin D in PCD. Both studies found no significant differences in pulmonary functions between patients with adequate and inadequate vitamin D supplementation. However, PCD patients suffer from frequent airway infections that could be exacerbated by low vitamin D's influence on the lung and overall immunity. Vitamin D supplements may not be considered facultative. It seems that vitamin D supplements should be regular during the first twelve months of life but only one-third of children should continue to receive the supplement beyond one year of age. From one perspective, details of patients' diet affected with PCD should represent the focus of studies in the future.

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Informed Consent Statement: Informed consent was obtained for nasal brushing for all subjects. Anonymous reproduction of the electron microscopy is permitted in manuscripts classified as reviews.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The author declares no conflict of interest.

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