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Vitamin D deficiency in Crohn's disease and healthy controls: A prospective case–control study in the Netherlands☆

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Abstract

Background and aims: Vitamin D deficiency has been observed in a wide range of medical conditions including Crohn's disease (CD). We aimed to assess whether CD patients have lower vitamin D levels than healthy controls, and to determine risk factors for vitamin D deficiency.
Methods: 25(OH)D was measured by chemiluminescent immunoassay in serum obtained from 101 CD patients and 41 controls. Demographics, sunlight exposure, dietary vitamin D intake, comorbidities and medication were recorded using validated questionnaires. In CD patients the Harvey–Bradshaw index, Montreal classification and surgical resections were also evaluated. 25(OH)D levels of >75 nmol/L, between 50 and 75 nmol/L and <50 nmol/L were considered as normal, suboptimal and deficient, respectively.
Results: Vitamin D levels were rather low but comparable among CD patients and controls (mean 25(OH)D 51.6 nmol/L(±26.6) in CD, and 60.8 nmol/L(±27.6) in controls. Multivariate regression analysis revealed BMI, sun protection behaviour, non-Caucasian ethnicity, no use of tanning beds, and no holidays in the last year as significantly associated with serum 25(OH)D levels in CD patients (R = 0.62). In the control group no statistically significant factors were identified that had an impact on 25(OH)D serum levels.
Conclusions: Vitamin D deficiency is common in CD patients, but also in healthy controls. Appropriate vitamin D screening should be advised in patients with CD. Moreover, the positive

Abbreviations: CD, Crohn's disease; 25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1.25-dihydroxyvitamin D; PTH, parathyroid hormone; UV, ultraviolet; HBI, Harvey–Bradshaw Index; CRP, C-reactive protein; IQR, inter quartile range; MS, multiple sclerosis; IL, interleukin; LC–MS/MS, liquid chromatography–tandem mass spectometry.

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effect of sunlight on the vitamin D status should be discussed with CD patients, but this should be balanced against the potential risk of developing melanomas, especially in patients using thiopurines.

1. Introduction

Vitamin D has recently become a topic of scientific attention. Vitamin D belongs to the group of fat-soluble secosteroids, which humans mainly obtain from ultraviolet B radiation from sunlight exposure. In small amounts it is acquired from the diet, mainly fatty fish like salmon or mackerel, fish oil, fortified milk/orange juice, margarine, and egg yolk. Vitamin D from both the skin and diet is metabolized in the liver to 25-hydroxyvitamin D (25(OH)D, calcidiol) and subsequently in the epithelial cells in the proximal tubule of the kidneys to the active form, 1.25-dihydroxyvitamin D ($1,25(OH)_2D$, calcitriol).[1,2]

The classic role of vitamin D is related to bone homeostasis.[1,3,4] Lately, however, vitamin D was also shown to be involved in various forms of cancer such as colorectal, prostate and breast cancer,[5] and it exerts anti-inflammatory and immunomodulating effects.[1,6,7] Vitamin D deficiency is more common in populations living at higher latitudes because of more limited sunlight exposure in these areas, in elderly and in women during pregnancy or lactation.[1] Finally, there is a seasonal variance in vitamin D levels, with lowest levels during the winter period.[8–10]

Hypovitaminosis D is common in patients with Crohn's disease (CD),[8,10–20] most probably due to a combination of different mechanisms such as malabsorption of vitamin D due to short gut syndrome (after surgery) or small bowel inflammation, intestinal loss due to protein losing enteropathy, decreased dietary intake, and limited exposure to sunlight.[1,2,21] Vitamin D is mostly absorbed in the small intestine and is subject to the enterohepatic circulation.[19,22,23]

Interestingly, the incidence of CD varies geographically with an increased incidence of CD with latitudes farther north and south of the equator. CD patients with less sunlight exposure have been reported to have lower serum 25(OH)D levels which is associated with more active disease, although a causal relationship has not been established.[2,24,25]

There has been an extensive discussion with regard to which cut-off values should be used for 'normal' and 'low' concentrations of vitamin D in standard and diseased populations. Vitamin D deficiency is often defined as a serum level of 25(OH)D that can lead to evident pathology, such as osteoporosis or rickets disease.[26,27] Vitamin D insufficiency refers to a serum level of 25(OH)D leading to increased parathyroid hormone (PTH) levels, which eventually leads to osteomalacia.[27] Previous studies on cut-off values however are based on bone mineral density instead of autoimmune diseases,[28,29] and laboratory target values vary greatly due to the lack of consensus on 25(OH)D ranges and different laboratory tests of measuring vitamin D serum levels.[2,30–32] Vitamin D levels are monitored as serum 25(OH)D, since it has a relatively long circulating half-life of approximately 10–15 days, and because it represents stores of vitamin D more reliably than active calcitriol.[33,34] The World Health Organization defines vitamin D deficiency as a 25(OH)D serum level below 50 nmol/L.[1,35,36] Levels $\leq$25 nmol/L are defined as 'severe deficiency' and levels $\leq$75 nmol/L as suboptimal.[20,27,35,37,38] In this article, we use the term "deficiency" to indicate at least suboptimal levels of $\leq$75 nmol/L.

In this prospective study, we aimed to assess whether CD patients have decreased levels of vitamin D compared to controls in an outpatient setting. Secondly, we investigated factors potentially contributing to vitamin D deficiency in both groups.

2. Methods

2.1. Study population

Adult patients ($\geq$18 years of age) with established CD were prospectively recruited at the Inflammatory Bowel Disease outpatient clinic of the Academic Medical Center, Amsterdam, The Netherlands (a tertiary referral center), during the fall (September–December 2012). Controls were healthy hospital employees visiting the department of occupational health, safety and environment and patients with functional oesophageal disorders without other bowel disorders. Subjects were only asked to participate if routine blood examination withdrawal was performed for other reasons. Subjects using vitamin D medication or multivitamin supplements were excluded from this study. No institutional ethical permission was required based on Dutch legislation.

2.2. Questionnaires

Subjects enrolled in this study received a standardized questionnaire, containing demographic data, sunlight exposure, dietary vitamin D intake, smoking habits and medication use. The sunlight exposure questions were based on a consensus-based set of questions on ultraviolet (UV) radiation exposure outlined by Glanz et al.[39] The skin colour (of the inner side of the upper arm, ranging in 5 steps between very fair and very dark), sunny or active holidays in the past year, tanning bed use, time spent outside in the summer between 10 am and 4 pm during the week and weekend on a normal day, and the use of sun protection during a regular sunny day (using sunscreen, wearing a T-shirt with long sleeves, covering of the head, staying in the shadow and wearing sunglasses) were studied. It has been shown that these self-reports of sun exposure are statistically significant valid measurements of UV exposure.[40] Each answer to the five questions on the sun protection behaviour could range between one (not at all using protection) to 5 (always using protection) points; therefore, the total score could range from 5 to 25 points. In addition, medical comorbidities, pregnancy and lactation were recorded. With the help

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