

# Vitamin D and Prolonged Treatment with Photosensitivity-Associated Antibiotics

Emmanouil Angelakis,<sup>a</sup> Christiane Oddoze,<sup>b</sup> Didier Raoult<sup>a</sup>

Unité de Recherche sur les Maladies Infectieuses et Tropicales Emergentes, URMITE CNRS-IRD 198 UMR 6236, Université de la Méditerranée, Faculté de Médecine, Marseille, France<sup>a</sup>; Clinical Laboratory, Laboratoire de Biochimie Endocrinienne, CHU Timone, Marseille, France<sup>b</sup>

Vitamin D has important roles in physiological processes and is primarily involved in calcium and phosphorus homeostasis and musculoskeletal system metabolism (1, 2). Moreover, vitamin D acts on the cardiovascular system and in systemic inflammation, oxidative stress, and immune regulation (1, 2). Vitamin D deficiency has been proposed as a risk factor for many diseases that are not traditionally associated with vitamin D and mineral metabolism, such as cancer, cardiovascular disease, hypertension, and diabetes (1, 2). In addition, studies have shown an inverse association between vitamin D and visceral adiposity (3).

Q fever is a worldwide zoonosis caused by *Coxiella burnetii* (4). Endocarditis is the most-serious complication of Q fever, and the optimal duration of treatment using doxycycline and hydroxychloroquine is 18 months for native valves and 24 months for prosthetic valves (5, 6). However, patients treated with doxycycline and hydroxychloroquine are not exposed to sunlight because they commonly present photosensitivity, including sunburn, photosensitive eruptions, blistering, rash, pruritus, and photonychia (7, 8). Our study was based on the experience of a medical doctor who was treated for 1 year with doxycycline and hydroxychloroquine and who notified one of us (D.R.) that he had found that he had a low level of vitamin D. The aim of this study was to investigate the levels of vitamin D in patients with treated Q fever endocarditis. We retrospectively compared the vitamin D levels of patients who were receiving doxycycline and hydroxychloroquine and a control group without antibiotic therapy.

This study was performed after ethical approval by the local ethics committee (accession number 10-002, 2010). Sera were obtained from the outpatients of an infectious disease unit (Hopital La Timone, Marseille, France) who were suffering from Q fever and treated with doxycycline (100 mg twice per day) and hydroxychloroquine (200 mg three times per day). Doses were adjusted monthly based on drug monitoring (0.8 to 1.2 mg/ml for hydroxychloroquine and >4.8 mg/ml for doxycycline) (5). Healthy individuals without antibiotic treatment for at least 6 months (Hopital La Timone, Marseille, France) were used as controls. The exclusion criteria were an age under 18 years, a history of cancer, inflammatory bowel disease or acute or chronic diarrhea in the previous 4 weeks, vitamin D administration, and the administration of another antibiotic >6 months before sampling. Total vitamin D (25-OH vitamin D<sub>2</sub> and 25-OH vitamin D<sub>3</sub>) concentrations were determined for each patient using the Liaison (DiaSorin, Stillwater, MN) automated competitive immunoassay. Three groups were identified, as follows: group I, doxycycline-hydroxychloroquine treatment for more than 3 months; group II, doxycycline-hydroxychloroquine treatment for less than 3 months; and group III, control (no antibiotic treatment). Vitamin D levels were calculated for all of the patients. For data comparison, we used EpiInfo version 6.0 (Centers for Disease Control and Preven-

TABLE 1 Population characteristics

Characteristic	Treated patients (n = 56)	Controls (n = 50)
No. with Q fever endocarditis	56	0
Doxycycline-hydroxychloroquine	Yes	No
Median age (yr) ± IQ range	52 ± 17	57 ± 14
No. (%) male	34 (60)	28 (61)

tion, Atlanta, GA, USA). A *P* value of <0.05 was considered significant.

Overall, we tested 106 patients, including 56 with Q fever endocarditis and 50 controls (Table 1). The median age ± interquartile range (IR) was 54 ± 15 years, and 57 (63%) were males. All patients with Q fever endocarditis were treated with doxycycline and hydroxychloroquine. Forty patients had been receiving treatment for less than 3 months at the time of sampling, and 16 patients had been receiving treatment for more than 3 months at the time of sampling. The vitamin D levels were significantly higher in the control group than in Q fever patients treated with doxycycline and hydroxychloroquine (*P* < 0.0001) (Fig. 1a). The duration of treatment was also associated with the level of vitamin D (*P* < 0.0001), and control patients presented significantly higher vitamin D levels than patients receiving doxycycline-hydroxychloroquine, whether for less than or for more than 3 months (*P* < 0.0001 and *P* < 0.0001, respectively) (Fig. 1b). Lastly, patients receiving treatment for more than 3 months presented significantly lower vitamin D levels than patients treated for less than 3 months (*P* = 0.01).

Our study demonstrates that doxycycline-hydroxychloroquine administration was associated with a significant reduction in vitamin D levels and that the duration of treatment also affected vitamin D levels. Low vitamin D levels have been associated with increased activation of the renin-angiotensin system, leading to elevated blood pressure and associated with increased cardiovascular disease (9). Meta-analysis results showed that higher levels of vitamin D among middle-aged and elderly populations were associated with a decrease in cardiovascular disease, type 2 diabetes, and metabolic syndrome (10). Recently, vitamin D deficiency was found to be a potential risk factor for obesity and the development of insulin resistance, leading to type 2 diabetes (11). Low vitamin D levels may contribute to obesity or inhibit weight loss (12),

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Address correspondence to Didier Raoult, didier.raoult@gmail.com.

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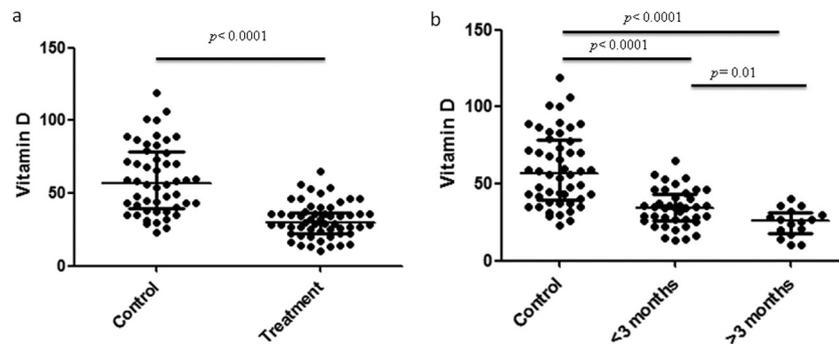


FIG 1 Vitamin D levels and (a) patients treated with doxycycline and hydroxychloroquine versus control group patients; (b) duration of treatment of patients treated with doxycycline and hydroxychloroquine versus control group patients.

although randomized controlled trials testing the effect of vitamin D supplementation on weight have provided inconsistent findings (9, 13). However, it was proposed that the vitamin D pathway genes are unlikely to play a major role in obesity-related traits in the general population (14).

In conclusion, we found in patients an association of vitamin D deficiency with long-term doxycycline-hydroxychloroquine treatment. The causation of this deficiency cannot be concluded from this work. Vitamin D is primarily produced in the skin by the action of sunlight (2), and possibly patients receiving doxycycline-hydroxychloroquine treatment are not exposed to sunlight because of photosensitization and thus present vitamin D deficiency. We propose that patients with long-term doxycycline-and-hydroxychloroquine treatment should be regularly tested, and in cases of vitamin D deficiency, treatment with a vitamin D supplement should be added.

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