AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Retraction for Angelakis et al., "Abnormal Weight Gain and Gut Microbiota Modifications Are Side Effects of Long-Term Doxycycline and Hydroxychloroquine Treatment"

American Society for Microbiology

The American Society for Microbiology (ASM) and *Antimicrobial Agents and Chemotherapy* (AAC) are issuing this retraction notice regarding the following publication:

> Angelakis E, Million M, Kankoe S, Lagier J-C, Armougom F, Giorgi R, Raoult D. 2014. Abnormal weight gain and gut microbiota modifications are side effects of long-term doxycycline and hydroxychloroquine treatment. Antimicrob Agents Chemother 58:3342–3347. https://doi.org/10.1128/AAC.02437-14.

Following the publication of the Expression of Concern at https://doi.org/10.1128/aac.00783-22, the University of Aix Marseille conducted an ethical assessment of this research article, for which the majority of the authors were also affiliated with IHU Méditerranée Infection. The ethics committee, comprising independent and international members, specifically evaluated participant recruitment for the study, sample collection, and if the authors had appropriate ethical approvals from the Institutional Review Board.

According to the investigation report, the information provided in the Materials and Methods section under "Patients," reading "This study received ethical approval through the local ethics committee (number 10–002, 2010)" is incorrect, and there remains doubt whether the decision actually covers the published study. Furthermore, this type of study falls "under the French law on the protection of research participants. Therefore, it should have been submitted to CPP (Committees of the Protection of Persons) ... Formally, this paper could not be deemed in conformity with the Declaration of Helsinki and the French Law and regulations."

In light of the severity of the research ethics breach indicated by these findings, and in accordance with COPE guidelines, this article is being retracted by ASM and AAC.

See the retracted article at https://doi.org/10.1128/aac.02437-14.

Published 4 January 2024

AAC Journals.ASM.org

Abnormal Weight Gain and Gut Microbiota Modifications Are Side Effects of Long-Term Doxycycline and Hydroxychloroquine Treatment

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Doxycycline has been proposed for the treatment of malnourished children in developing countries, and its use has been associated with weight gain in healthy volunteers. No previous studies have assessed abnormal weight gain as a putative side effect of long-term doxycycline treatment; thus, the objective of the present study was to characterize this phenomenon. We also analyzed the role of the gut microbiota in this effect. We assessed changes in the body mass index in Q fever endocarditis patients treated with doxycycline and hydroxychloroquine and healthy individuals with no antibiotic treatment. Abnormal weight gain was defined as a gain in weight above that of the controls. The fecal samples were examined using molecular assays for *Methanobrevibacter smithii*, *Bacteroidetes*, *Firmicutes*, *Escherichia coli*, *Lactobacillus*, *Lactobacillus reuteri*, and total bacterial concentrations. We examined 82 patients, including 48 patients with Q fever endocarditis and 34 controls. Approximately 23% of the treated patients showed abnormal weight gain ($P = 0.001$). Patients treated with doxycycline and hydroxychloroquine presented significantly lower concentrations of *Bacteroidetes* ($P = 0.002$), *Firmicutes* ($P = 0.01$), and *Lactobacillus* ($P = 0.02$). The linear regression analysis revealed that the duration of treatment was significantly associated with a decrease in *Bacteroidetes* ($P = 0.0001$), *Firmicutes* ($P = 0.002$), and total bacteria ($P < 0.00001$). Abnormal weight gain is a side effect of long-term doxycycline and hydroxychloroquine treatment. Gut microbiota modifications at the phylum level could play an instrumental role in this effect. We highlight the need for specific nutritional care in patients undergoing long-term antibiotic treatment, particularly treatment involving the use of doxycycline.

Obesity is a major public health challenge of the 21st century, and this condition has been associated with the elimination of some bacterial groups and reduced bacterial diversity in the microbiota (1). In combination with dietary changes, antibiotic administration has been associated with changes in the population structure of the gut microbiota. The oral administration of antibiotics, in either feed or water, suggests that the microbiota of the gastrointestinal tract is a major target (2). Many different classes of antibacterial agents, including macrolides, tetracyclines, and penicillins, promote animal growth. In contrast, these effects have not been demonstrated as antifungals or antivirals (2). Antibiotics significantly reduce gut bacteria, and in certain patients, these medicines completely eliminate specific bacterial communities (3). Although modifications to the gut microbiota resolve following short-term antibiotic therapy, long-term therapy can result in pervasive alterations (4). In humans, antibiotic treatment is commonly used as complement therapy for malnutrition (5, 6), leading many researchers to reconsider the impact of the antibiotics administered during early infancy for the treatment of obesity in childhood (7). In addition, vancomycin has been associated with reduced microbial diversity (8), weight gain, and acquired obesity in adults (9, 10).

Chlortetracycline has been used in livestock agriculture to promote growth through increased food intake, weight gain, and improved herd health (11). Since the 1940s, tetracyclines have been associated with weight gain in human infants and children (12), and one study showed significant weight gain in adults (13). Chlortetracycline has been recently associated with a decrease in the *Bacteroidetes*/*Firmicutes* ratio, increased adiposity, and metabolic alterations in young mice (2). The tetracycline antibiotic doxycycline, in combination with hydroxychloroquine (OHCQ), is recommended for the long-term treatment of Q fever endocarditis: 18 months for native valves and 24 months for prosthetic valves (14, 15). At a WHO reference center for Q fever, a member of our group (D.R.) regularly monitored more than 200 Q fever endocarditis patients undergoing long-term doxycycline and OHCQ treatment (14) over the last 20 years. Notably, involuntary weight gain has been reported in some patients, thereby motivating the objective of this study. Similar cases of acquired obesity have been previously associated with the eradication therapy for *Helicobacter pylori* (16, 17). Thus, the aim of this study was to investigate the effects of oral therapy with doxycycline and OHCQ on weight and the gut microbiota in humans, comparing Q fever endocarditis patients with healthy controls.

MATERIALS AND METHODS

Patients. Q fever endocarditis patients (18) were treated at an outpatient clinic (Hospital La Timone, Marseille, France) from 2008 to 2011 using a combination of doxycycline (100 mg twice a day) and OHCQ (600 mg daily) for at least 18 months according to current recommendations (14). The controls included healthy individuals consulting as outpatients in the infectious disease unit at Hospital La Timone (Marseille, France), and these patients had not received antibiotic treatment for at least 1 year. The

Received 4 February 2014 Returned for modification 2 March 2014
Accepted 24 March 2014
Published ahead of print 31 March 2014
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Supplemental material for this article may be found at http://dx.doi.org/10.1128/AAC.02437-14.

doi:10.1128/AAC.02437-14

inclusion criteria were adult patients for whom the body mass index (BMI) value and a fecal sample were available. The exclusion criteria were patients under 18 years old with acute or chronic diarrhea in the previous 4 weeks, a history of colon cancer, bowel inflammatory disease, and treatment with another antibiotic in the 6 months before fecal sampling. The data (gender, date of birth, clinical history, weight, weight before disease, height, antibiotic use, and significant changes in diet) were recorded using a standardized questionnaire, and no patient received antiobesity intervention during the follow-up. Three groups were identified for fecal sample analysis: doxycycline and OHCQ treatment for more than 3 months, doxycycline and OHCQ treatment for less than 3 months, and no antibiotic treatment for at least 1 year (controls). "Lean" was defined as patients with a body mass index (BMI) of 18 to 20 kg/m^2, "normal" was defined as patients with a BMI of 20 to 25 kg/m^2, "overweight" was defined as patients with a BMI of 25 to 30 kg/m^2, and "obese" was defined as patients with a BMI of >30 kg/m^2. The percentage of change in BMI (% ΔBMI) was calculated by the following formula: % ΔBMI = [(BMI at 1 year − baseline BMI)/baseline BMI] × 100. Acquired obesity was defined as patients with a BMI of >30 kg/m^2 after 1 year compared with a BMI of <30 at baseline. This study received ethical approval through the local ethics committee (number 10-002, 2010).

Abnormal weight gain. Abnormal weight gain was defined as a weight gain at 1 year (according to the % ΔBMI) not observed in the controls.

Abnormal weight loss. Abnormal weight loss was defined as a weight loss at 1 year (according to the % ΔBMI) not observed in the controls.

Molecular assay. The stool samples, collected using sterile plastic containers, were immediately transported to the laboratory and frozen at −80°C until further analysis. The DNA was isolated from the stool as previously described (19). The purified DNA samples were diluted to a final volume of 100 ml and stored at −80°C until further analysis. Real-time PCR for *Methanobrevibacter smithii*, *Bacteroidetes*, *Firmicutes*, *Lactobacillus*, *Lactobacillus reuteri*, *Escherichia coli*, and total bacteria was performed on a Stratagene MX3000 system (Agilent, Santa Clara, CA) using the QuantiTect PCR mixture (Qiagen, Courtaboeuf, France) and primers as previously described (20, 21).

Statistical analysis. The proportions were compared using two-sided chi-square and Barnard's exact tests (22). The distribution was typically not normal for quantitative comparisons, and thus, one-way analysis of variance (ANOVA) and the Kruskal-Wallis and Mann-Whitney tests were used to compare the weight changes and bacterial concentrations between the treatment groups. For the gut microbiota analysis, multiple comparisons were planned *a priori*, comparing controls versus treatment, controls versus treatment for less than 3 months, controls versus treatment for more than 3 months, and treatment for more than 3 months versus treatment for less than 3 months. Significant results were systematically confirmed using Dunn's multiple-comparison test. Linear regression analysis, adjusted systematically for age and BMI, was used to estimate the effect of treatment duration on *Bacteroidetes*, *Firmicutes*, and total bacteria. (The hypotheses underlying this model were not verified for *M. smithii* and *Lactobacillus*.) All tests were bilateral and considered significant at $P < 0.05$. The analyses were performed using SPSS v21.0 (IBM, Paris, France), R version 2.14.0 (R-foundation, Vienna, Austria), and XLSTAT v12 (Addinsoft, Paris, France) software.

RESULTS

We examined a total of 82 individuals, including 48 patients with Q fever endocarditis and 34 controls (62% males; mean age ± [SD], 57 ± 15 years). The mean age ± SD was 55 ± 15 years, and the study group included 49 (60%) males. Thirty-four patients (56% males; mean age ± SD, 51 ± 15 years) received doxycycline treatment for less than 3 months at the time of sampling, and 14 patients (64% males, mean age ± SD, 57 ± 14 years) received treatment for more than 3 months at the time of sampling. No significant difference was observed for age and sex among the three groups tested ($P = 0.08$ and $P = 0.8$, respectively).

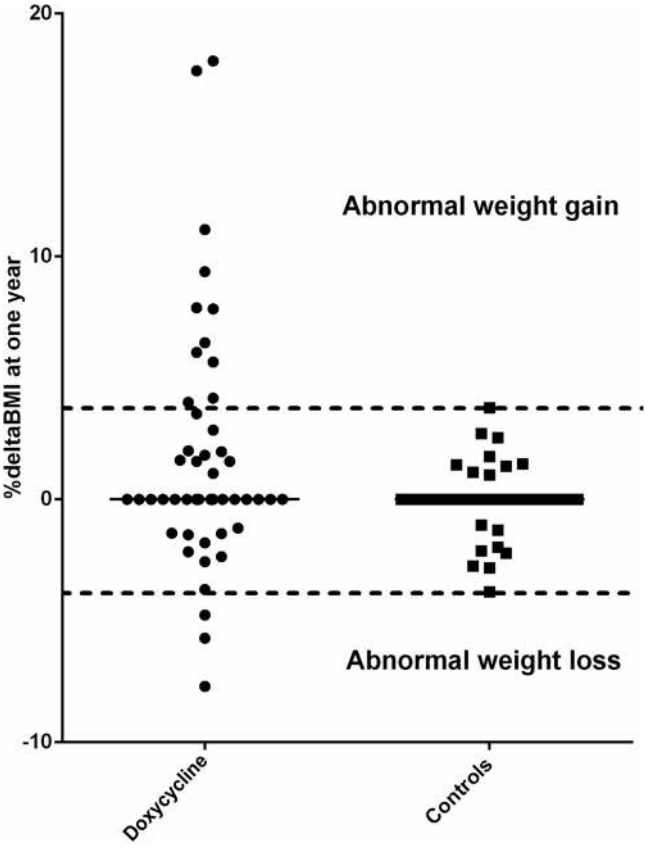

FIG 1 Abnormal weight gain in patients with prolonged doxycycline and OHCQ treatment and controls. An abnormal weight gain was defined as weight gain at 1 year (assessed by the % ΔBMI) not found in controls.

Doxycycline and changes in weight. We observed that 11/48 (23%) treated patients showed abnormal weight gain (+2 to +13 kg, corresponding to +4% to +18% ΔBMI), and this proportion was significantly different from that in the controls (0/34 [0% according to our definition]; $P = 0.001$, two-sided Barnard's test) (Fig. 1). We also observed that three of the treated patients (6%) exhibited abnormal weight loss, but this proportion was not different from that in the controls (0/34 [0% according to our definition]; $P = 0.16$, two-sided Barnard's test). The treated population showed no significant difference in weight change at 1 year compared with the controls (data not shown), suggesting that only specific subgroups are at risk for side effects associated with abnormal weight gain and abnormal weight loss.

Gut microbiota alterations following antibiotic treatment. (i) *Bacteroidetes*. *Bacteroidetes* were detected in all samples analyzed. Compared with the controls, *Bacteroidetes* were detected at lower concentrations in the treated group ($P = 0.002$) (Fig. 2), patients treated for less than 3 months at the time of sampling ($P = 0.01$, Mann-Whitney test), and patients treated for more than 3 months at the time of sampling ($P = 0.003$, Mann-Whitney test). These results were confirmed using Dunn's multiple-comparison test. There was no significant difference between the patients treated for more than 3 months and those treated for less than 3 months at the time of sampling, but the duration of treat-

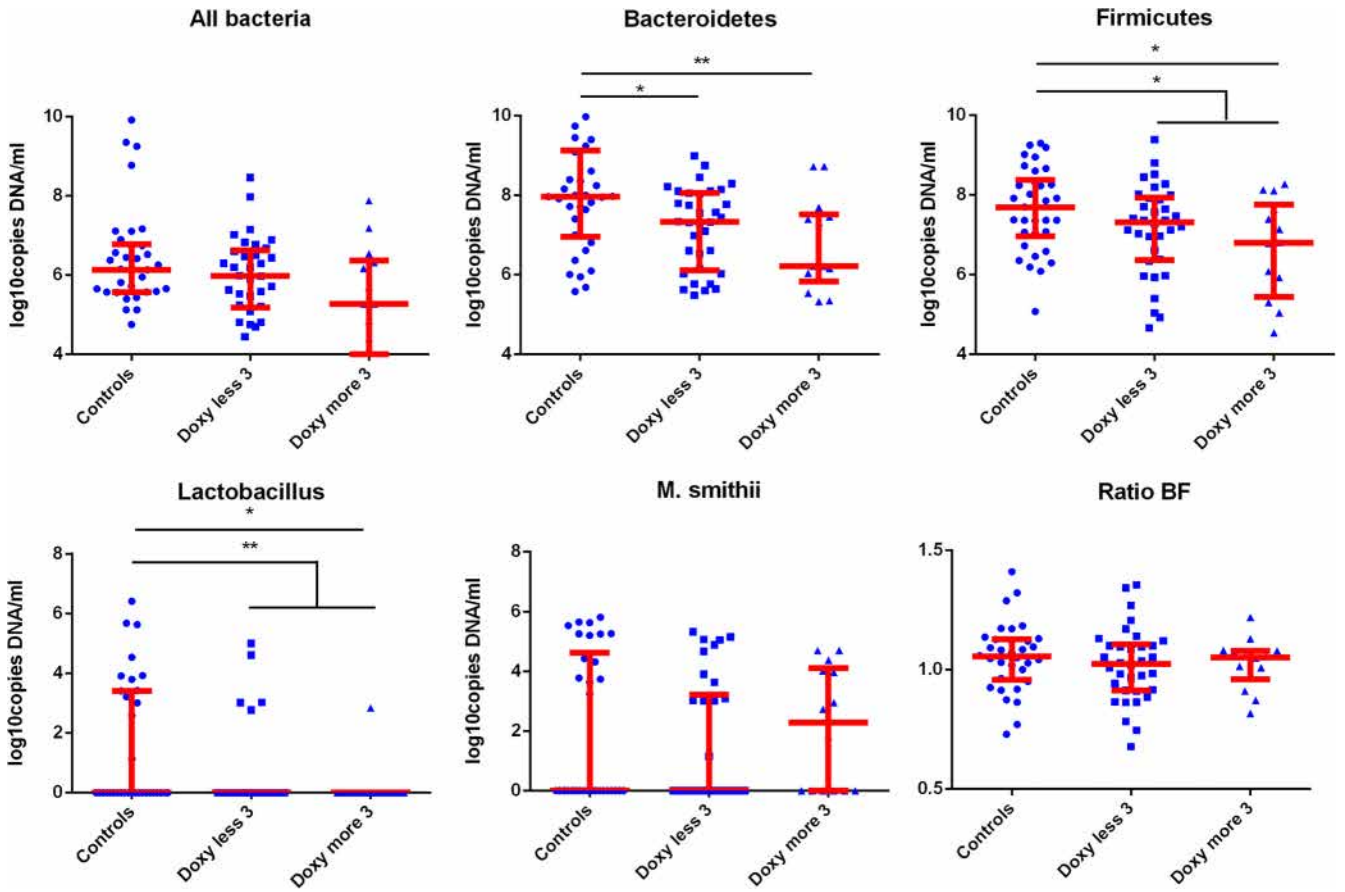

FIG 2 Gut microbiota alteration associated with doxycycline and OHCQ treatment. *, $P < 0.05$; **, $P < 0.005$. Patients treated with doxycycline (doxy) and hydroxychloroquine presented significantly lower concentrations of *Bacteroidetes* ($P = 0.002$), *Firmicutes* ($P = 0.01$), and *Lactobacillus* ($P = 0.02$). Linear regression analysis revealed that the duration of treatment was significantly associated with a decrease in *Bacteroidetes* ($P = 0.0001$), *Firmicutes* ($P = 0.002$), and total bacteria ($P < 0.00001$).

ment was associated with a decrease in the *Bacteroidetes* population based on the linear regression analysis ($P = 0.0001$) (Table 1).

(ii) *Firmicutes.* *Firmicutes* were detected in all samples analyzed. Compared with controls, the *Firmicutes* population was significantly decreased in patients treated with doxycycline for more than 3 months ($P = 0.01$, Mann-Whitney test [confirmed using Dunn's multiple-comparison test]) and in all treated patients ($P = 0.02$, Mann-Whitney test) (Fig. 2). The linear regression analysis revealed that the concentration of *Firmicutes* decreased according to the treatment duration ($P = 0.002$) (Table 1).

(iii) *Lactobacillus.* Compared with controls, the prevalence of *Lactobacillus* was decreased in treated patients (6/48 versus 13/34; $P = 0.006$, bilateral Barnard's test), patients treated for less than 3 months (5/34 versus 13/34; $P = 0.03$, Barnard's test), and patients treated for more than 3 months ($P = 1/14$ versus 13/34; $P = 0.006$, Barnard's test) (see Fig. S1 in the supplemental material). There

TABLE 1 Effect of treatment duration on the gut microbiota[a]

Covariate	*Bacteroidetes*		*Firmicutes*		Total bacterial count	
	Coefficient (95% CI)[b]	*P* value	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value
Treatment duration						
No treatment	0		0		0	
<3 mo	−0.7 (−1.3 to −0.2)	0.007	−0.4 (−0.9–0.1)	0.1	−0.5 (−1.1–0.09)	0.1
>3 mo	−1.3 (−2.0 to −0.7)	0.0001	−1.0 (−1.7 to −0.4)	0.002	−1.2 (−2.0 to −0.5)	0.001
Age	0.02 (0.004–0.03)	0.01	0.01 (0.002–0.03)	0.02	0.01 (−0.006–0.02)	0.2
Intercept	6.2 (4.3–8.0)	2.7e−9	5.9 (4.1–7.6)	2.0e−9	6.4 (4.3–8.4)	1.7e−8

[a] Multiple regression analyses were performed for each bacterial clade systematically adjusted according to the BMI.
[b] 95% CI, 95% confidence interval.

was no significant difference between patients treated for more than 3 months and those treated less than 3 months.

The *Lactobacillus* concentration was decreased in patients receiving doxycycline treatment for more than 3 months compared with controls ($P = 0.02$, Mann-Whitney test [confirmed using Dunn's multiple-comparison test]) (Fig. 2). The concentration of *Lactobacillus* was significantly lower in treated patients than that in controls ($P = 0.004$, Mann-Whitney test).

(iv) *Lactobacillus reuteri*. We tested 53 patients, and *Lactobacillus reuteri* was observed in 2 (4%) individuals. Both patients received doxycycline treatment for less than 3 months, and there was no difference in the % ΔBMI between these individuals.

(v) *Methanobrevibacter smithii*. *Methanobrevibacter smithii* was observed in 36/82 individuals (44%). The prevalences were not significantly different between each group (15/34 [44%] in controls, 16/34 [47%] in patients with less than 3 months of doxycycline, and 5/14 [36%] in patients with more than 3 months of doxycycline) (see Fig. S1 in the supplemental material). The concentrations of *M. smithii* were not significantly different between treated patients and controls (Fig. 2).

(vi) *Escherichia coli*. We tested 53 patients, and *Escherichia coli* was observed in 21 (40%) individuals. The prevalences were not significantly different between each group (9/21 [42%] in controls, 8/20 [40%] in patients with less than 3 months of doxycycline, and 4/12 [33%] in patients with more than 3 months of doxycycline). The concentrations of *E. coli* were not significantly different between treated patients and controls ($P = 0.4$).

(vii) *Firmicutes*/*Bacteroidetes* ratio. Treatment did not affect the *Firmicutes*/*Bacteroidetes* ratio ($P = 0.32$, Mann-Whitney test comparing treated versus untreated, and $P = 0.60$, Kruskal-Wallis test for all three groups).

(viii) Total bacteria. The total bacterial gut content was decreased with doxycycline treatment (Fig. 2), but this effect was not significant ($P = 0.09$ for three groups, Kruskal-Wallis test, and $P = 0.08$ for treated versus controls, Mann-Whitney test). The concentration was decreased in patients treated for more than 3 months compared with that in controls ($P = 0.03$, Mann-Whitney test), but this result was not confirmed using Dunn's multiple-comparison test. As shown in the graph in Fig. 2, the amount of total bacterial was reduced in patients treated with doxycycline for more than 3 months compared with those treated for less than 3 months. Moreover, the linear regression analysis revealed that the total bacterial concentration significantly decreased with treatment duration ($P < 0.00001$) (Table 1).

DISCUSSION

The results of the present study demonstrate abnormal weight gain as a side effect of long-term treatment with doxycycline and hydroxychloroquine. Moreover, doxycycline and hydroxychloroquine treatment exhibits a reproducible effect on the community structure of the gastrointestinal microbiota in humans. The reduction in bacteria was associated with the treatment duration, reinforcing the hypothesis of a causal relationship between this treatment and gut microbiota depletion, suggested to play an instrumental role in the weight gain side effect. We focused on the effect of long-term treatment with doxycycline over a 12-month period, as the patients examined in the present study were typically treated for at least 18 months. We specifically compared the weight after 1 year of antibiotic treatment with the weight before the disease. We did not consider the weight at endocarditis diagnosis, as this value is expected to be lower. Moreover, with the improvement and decrease of the delay in Q fever endocarditis diagnosis, weight loss is becoming less frequent (23), being reported in less than 50% of patients (14).

One in four treated patients presented abnormal weight gain, suggesting that long-term doxycycline treatment leads to significant changes in weight in specific subgroups of treated individuals. These results suggest that initial gut microbiota, which play an instrumental role in this effect, could predict abnormal weight gain after doxycycline treatment, as demonstrated in humans for *E. coli* and vancomycin (21) and in animal models for tetracycline (24). These results are consistent with previous studies showing that doxycycline is associated with weight gain in undernourished children in developing countries (25, 26) and in healthy U.S. army recruits (13). However, to our knowledge, this study provides the first assessment of weight gain as a side effect in patients receiving long-term doxycycline treatment for infection and not as a positive effect in children treated with chlortetracycline for malnutrition.

The long-term oral administration of doxycycline has been associated with a significant decrease in *Bacteroidetes*, *Firmicutes*, *Lactobacillus*, and the total intestinal bacterial content. Changes in weight have typically been associated with a specific profile of bacterial gut microbiota, including a decrease in the *Firmicutes*/*Bacteroidetes* ratio and decreased bacterial diversity (27). *M. smithii* is the dominant methanogenic archaeon species in the human microbiota and has been associated with weight modifications (28). Recently, the level and extent of *M. smithii* colonization were demonstrated as predictive of the degree of weight gain in an animal model (29). In addition, *Lactobacillus* and particularly *L. reuteri* have been associated with obesity, whereas *E. coli* has been associated with weight modifications (9, 20, 21). However, in the present study, no differences in the concentrations of *L. reuteri*, *E. coli*, and *M. smithii* between treated patients and controls were observed. Further analyses are needed to determine whether this global antibiotic-associated bacterial depletion and bacterial diversity reduction are advantageous for specific doxycycline-resistant bacteria associated with weight gain.

The quinine derivative hydroxychloroquine is an antimalarial drug primarily used in rheumatology to treat systemic lupus erythematosus and rheumatoid arthritis. The administration of hydroxychloroquine leads to the alkalinization of intracellular acid vesicles that inhibit the growth of several intracellular organisms, facilitating antibiotic efficacy for *Coxiella burnetii* and *Tropheryma whipplei* (14, 30). Moreover, *in vitro* data have suggested that the effects of hydroxychloroquine might be generalized for *Borrelia burgdorferi* (31) and all intracellular organisms that multiply in acidic environments (32). Although antimalarials are generally inactive against most extracellular bacterial species (33), a direct antibacterial effect has been demonstrated, with an *in vitro* inhibitory effect on the bacterial DNA polymerase of *E. coli* and *Micrococcus luteus* (34, 35). However, the results of a recent study indicated that quinine did not show any antibacterial activity against *E. coli* (33). The effects of hydroxychloroquine and its association with doxycycline on the gut microbiota have not been elucidated; however, considering the results of *in vitro* studies, the antibacterial spectrum of hydroxychloroquine is not significant compared with doxycycline activity.

In conclusion, the results of the present study showed that treatment with doxycycline is associated with abnormal weight

gain in humans, and this effect has been recently recognized as an important side effect of this antibiotic in one out of four treated patients. The modifications of the gut microbiota following doxycycline treatment might reflect direct antibacterial effects on the bacterial population or indirect effects that promote the growth of antibiotic-resistant bacteria. Previous studies have suggested that gut microbiota depletion at the phylum level might play an instrumental role in the occurrence of abnormal weight gain, but further studies are needed to clarify this correlation. It has recently been proposed that patients treated with *H. pylori* eradication therapy should be advised of the possibility of weight gain (16, 17). The results obtained in the present study demonstrate the risk of abnormal weight gain during long-term treatment with doxycycline for diseases such as Q fever endocarditis and highlight the need for specific nutritional care in patients receiving long-term antibiotic treatment, particularly for treatment with doxycycline.

ACKNOWLEDGMENTS

This study was funded through the French National Referral Center for Q Fever.

The authors declare they have no conflicts of interest.

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