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The Effect of Various Doses of Oral Vitamin D_3 Supplementation on Gut Microbiota in Healthy Adults: A Randomized, Double-blinded, Dose-response Study

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Abstract. *Background/Aim: To investigate the effects of vitamin D_3 supplementation on gut microbiota. Patients and Methods: Twenty adults with vitamin D insufficiency/deficiency [25(OH)D <30 ng/ml] were enrolled and given 600, 4,000 or 10,000 IUs/day of oral vitamin D_3. Stool samples were collected at baseline and 8 weeks for identifying gut microbiota using 16S rRNA gene amplification and sequencing. Results: Baseline serum 25(OH)D was associated with increased relative abundance of Akkermansia and decreased relative abundance of Porphyromonas ($p<0.05$). After the intervention, we observed a dose-dependent increase in relative abundance of Bacteroides with a significant difference between the 600 IUs and the 10,000 IUs groups ($p=0.027$), and Parabacteroides with a significant difference between the 600 IUs and the 4,000 IUs groups ($p=0.039$). Conclusion: Increased serum 25(OH)D was associated with increased beneficial bacteria and decreased pathogenic bacteria. A dose-dependent increase in bacteria associated with decreased inflammatory bowel disease activity was observed after vitamin D_3 supplementation.*

Vitamin D plays an essential role in regulating calcium and phosphate metabolism and maintaining healthy mineralized skeleton (1). Observational studies have suggested that high serum 25-hydroxyvitamin D [25(OH)D] is associated with a variety of extra-skeletal outcomes, including increased longevity and prevention of cardiovascular diseases, metabolic syndrome, cancers, and autoimmune diseases (1-3). However, whether or not the causality can be drawn from this association is largely controversial, and through which mechanisms does vitamin D exert its extra-skeletal effects is still unclarified.

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It has been suggested that alteration in gut microbiota is one of the mechanisms that link vitamin D with some of its extra-skeletal clinical outcomes. Variation in gut microbiota has been linked with a number of physiological functions, including absorption and metabolism of nutrients, immune regulation, and biosynthesis of neurotransmitters and hormones (4). The probable mechanism by which vitamin D may affect gut microbiota is mainly mediated by the biologic effect of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], the active form of vitamin D, on host immune response (4, 5). 1,25$(OH)_2$D induces macrophages to produce antimicrobial peptides, resulting in bacterial killing. On the other hand, 1,25$(OH)_2$D also modulates cell-mediated immune response by inhibiting proliferation of T cells, inducing a shift from Th1 to a Th2 development, suppressing interferon-γ and interleukin-17 producing T cells, facilitating T regulatory cells, thereby decreasing inflammatory activity against certain bacteria (4, 5).

Evidence on the effect of vitamin D supplementation on human gut microbiome is relatively limited. There are a few clinical trials including randomized and non-randomized interventional studies reporting inconsistent results, although most of them reported significant changes in certain bacteria (6-10). Therefore, as of now, the effect on vitamin D on human gut microbiota is still undetermined and inconclusive. The aim of this study was to investigate the effects of various doses of oral vitamin D_3 supplementation on the composition of gut microbiota in healthy adults. This will provide some perspective on how vitamin D could possibly exert extra-skeletal effects through alterations of gut microbiota.

Patients and Methods

Healthy adults who had vitamin D insufficiency/deficiency [25(OH)D<30 ng/ml] were enrolled in a randomized, double-blinded, investigator initiated, pilot study. This study investigated broad gene expression changes in peripheral blood mononuclear cells following vitamin D_3 supplementation of 600, 4,000 or 10,000 IU/day of vitamin D_3, as previously described (11). The study was

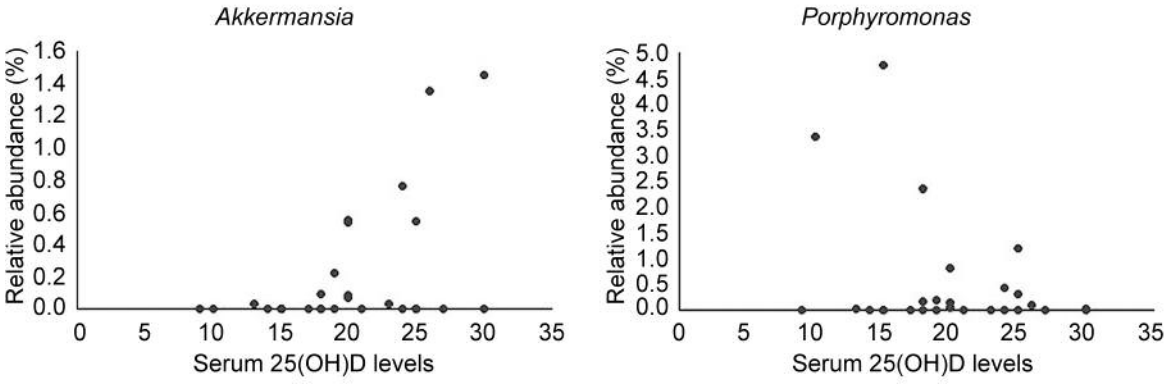

Figure 1. *Relative abundance of Akkermansia spp. (left) and Porphyromonas spp. (right) of the participants at various levels of serum 25(OH)D at baseline of the study.*

approved by the Boston University Medical Campus Institutional Review Board (NCT01696409, H-35506).

Stool microbiota assessment. Stool samples were collected at baseline of the study and at 8 weeks after vitamin D supplementation using Explorer™ Microbiome Sampling Kit. Samples were subsequently sent for microbiome analysis using 16S rRNA gene amplification and sequencing at uBiome Inc., (San Francisco, CA, USA). Data are reported as inverse Simpson diversity index and the relative abundance of a set of microbial taxa known to be associated with health conditions, as previously described (12).

Statistical analysis. Data were expressed as mean±standard deviation (SD). Pearson correlation analysis was used for determining correlation between two parametric continuous variables. Differences in relative abundance of each bacteria before and after the intervention were analyzed using paired T-test. Comparisons in changes in relative abundance of bacteria among the different arms were analyzed using one-way analysis of variance (ANOVA), followed by post hoc least significant difference (LSD) test to estimate the pairwise significance of difference. All statistical analyses were performed using a Statistical Package for the Social Sciences (SPSS) version 25.

Results

Among the 33 participants who were enrolled in the study, a total of 20 participants had fecal microbiome data for analysis (600 IU/day, N=7; 4,000 IU/day, N=7; 10,000 IU/day, N=6). After 8 weeks of the study intervention, participants receiving 600 IUs/day raised their serum 25(OH)D levels from 16.9±6.0 ng/ml to 20.0±3.4 ng/ml although without statistical significance (p=0.153). Participants receiving 4,000 IUs/day raised their serum 25(OH)D levels from 20.3±6.3 ng/ml to 39.0±8.7 ng/ml (p=0.01). Participants receiving 10,000 IUs/day raised their serum 25(OH)D levels from 18.5±3.5 ng/ml to 67.3±3.1 ng/ml (p<0.001).

As shown in Figure 1, we observed that baseline serum 25(OH)D levels were significantly positively correlated with relative abundance of *Akkermansia* spp. (R=0.684, p=0.001), and negatively correlated with relative abundance of *Porphyromonas* spp. (R=-0.435, p=0.043). We also observed a significant positive correlation between serum 25(OH)D and phylum Verrucomicrobia (R=0.680, p=0.001). In addition, there is a significant positive correlation between serum parathyroid hormone and relative abundance of *Bacteroides* spp. (R=0.535, p=0.012, Figure 1B), *Campylobacter* spp. (R=0.564, p=0.008), Family Enterobacteriaceae (R=0.468, p=0.032), class Gammaproteobacteria (R=0.538, p=0.012), and Bacteroidia (R=0.484, p=0.026), phylum Bacteroidetes (R=0.490, p=0.024), and Proteobacteria (R=0.584, p=0.005). There is a significant negative correlation between serum parathyroid hormone and relative abundance of class Negativicutes (R=–0.510, p=0.018) and Clostridia (R=–0.513, p=0.017), and phylum Firmicutes (R=–0.545, p=0.011).

Figure 2 demonstrates the relative abundance of each bacterial genus before and after 8 weeks of intervention in all participants regardless of arm. After 8 weeks of intervention, we found a statistically significant decrease in the relative abundance of *Faecalibacterium* spp., class Clostridia and family Ruminococcaceae (p<0.05 all). Moreover, we observed a significant decrease in Firmicutes to Bacteroidetes (F/B) ratio (2.9±1.6 to 1.9±1.0, p=0.024). Alpha-diversity did not significantly change in any group after the 8-week intervention.

Figure 3 demonstrates the comparisons of changes in relative abundance of each bacterial genus among the three arms of different doses of vitamin D_3. We observed a dose-dependent increase in relative abundance of *Bacteroides* spp. with a statistically significant difference between the 600 IUs group and the 10,000 IUs group (p=0.027). Moreover, a similar dose-dependent increase in relative abundance of

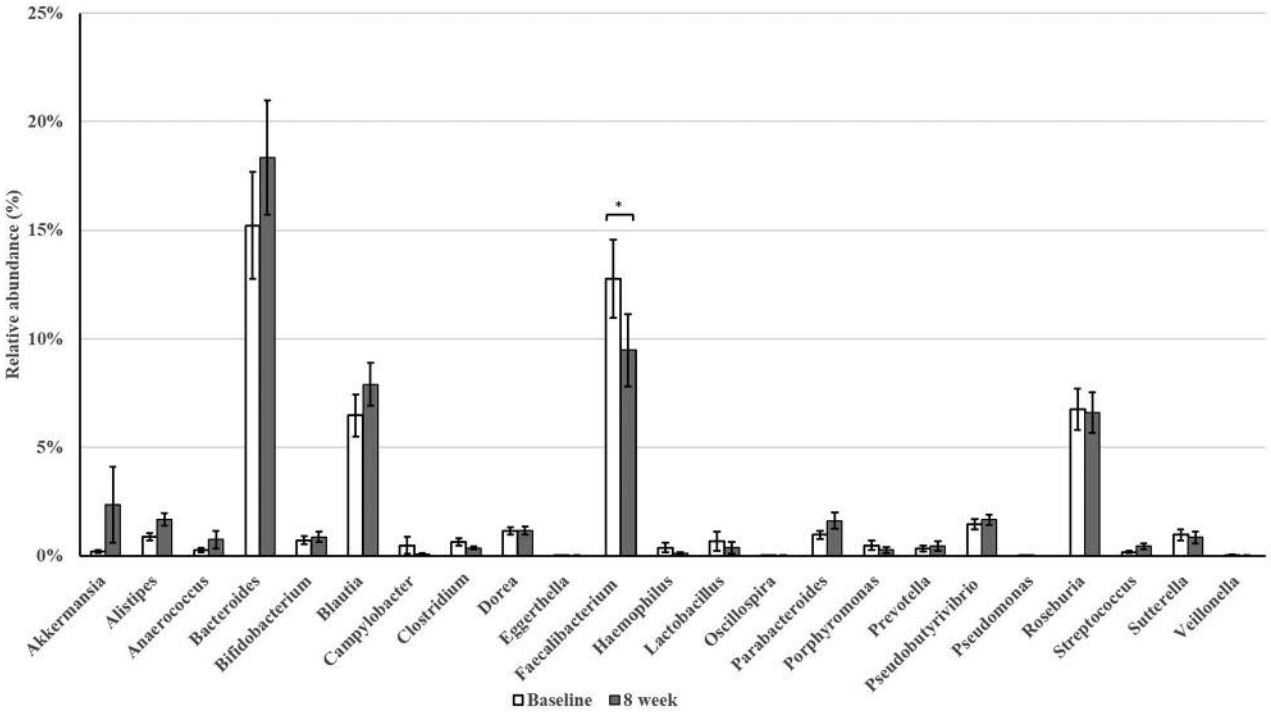

Figure 2. *Relative abundance of clinically relevant bacterial genera before and after 8 weeks of intervention in all participants. Data are expressed as mean±SEM.*

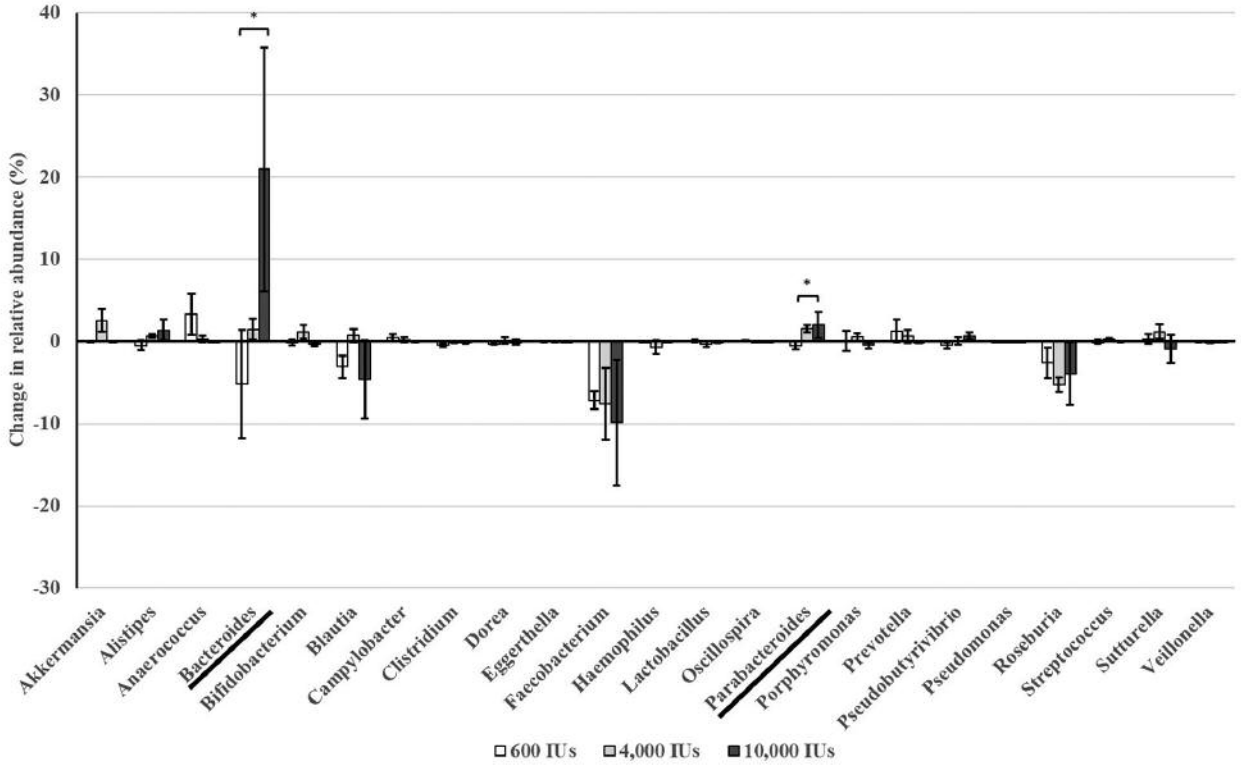

Figure 3. *Changes in relative abundance of clinically relevant bacterial genera in participants receiving 600 IUs/day (left), 4,000 IUs/day (middle), and 10,000 IUs/day (right) of vitamin D3 for 8 weeks. Data are expressed as mean±SEM.*

Parabacteroides spp. was observed with a statistically significant difference between the 600 IUs group and the 4,000 IUs group (p=0.039).

Discussion

Vitamin D is known to modulate innate and adaptive immune response through several mechanisms. Monocytes express the enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) that converts 25(OH)D into the active form of $1,25(OH)_2D$, which induces macrophages to produce antimicrobial peptides, resulting in bacterial killing (5). $1,25(OH)_2D$ also modulates T cell functions by inhibiting T cell proliferation, inducing a shift from Th1 to a Th2 development, suppressing Th17 cell development and facilitating regulatory T cells (5). Therefore, it is likely that vitamin D, by modulating host immune response against certain bacteria, may affect the composition of gut microbiota. To investigate this, we conducted a randomized, double-blinded, dose-response, pilot study aiming to determine the effects of various doses of oral vitamin D_3 (600 IUs/day, 4,000 IUs/day, and 10,000 IUs/day) on gut microbiota in healthy adults. Correlation analysis at baseline of the study showed that the relative abundance of a variety of bacteria are associated with serum 25(OH)D and PTH levels. After the 8-week intervention, we observed a statistically significant decrease in Firmicutes to Bacteroidetes ratio in all subjects and significant dose-dependent increase in relative abundance of *Bacteroides* spp. and *Parabacteroides* spp. These results provided some insight into how vitamin D status is possibly related to several clinical outcomes *via* its interaction with gut microbiota.

We observed that baseline serum 25(OH)D levels were positively correlated with relative abundance of *Akkermansia* spp. (R=0.684, p=0.001). This result is consistent with an observation by Su *et al*. that vitamin D receptor knockout mice as well as vitamin D deficient mice receiving high fat diet had diminished gut *Akkermansia muciniphila* (13). Increased richness of *Akkermansia muciniphila* has been shown to be associated with decreased risk of cancer, obesity and atherosclerosis, as well as improved fasting plasma glucose, plasma triglycerides and body fat mobilization (14-16). This is possibly mediated by its interaction with the intestinal epithelium causing improvement of gut barrier function and decreased metabolic endotoxemia (14-16). The increased relative abundance of this bacteria in association with higher serum 25(OH)D level, therefore, could be another explanation for how vitamin D is related to cardio-metabolic disorders and cancers. After vitamin D treatment for 8 weeks, regardless of dosage, a significant decrease in F/B ratio was observed. High F/B ratio has been linked to obesity and poor glycemic control (17). This may be another mechanism explaining the possible relationship between vitamin D deficiency and obesity, insulin resistance, and metabolic syndrome (18).

We found an inverse correlation between 25(OH)D levels and relative abundance of *Porphyromonas* spp., which is supportive of the finding by Grenier *et al*. (19) that $1,25(OH)_2D$ could directly inhibit growth and expression of the virulence factor of *Porphyromonas gingivalis*, a causative organism of chronic periodontitis. This finding could not only explain the link between vitamin D deficiency and periodontitis reported in several observational studies (20), but also supports the result from a randomized clinical trial by Hiremath *et al*. which has demonstrated the possible benefit of vitamin D in treating gingivitis (21).

We observed a substantial dose-dependent increase in the relative abundance of *Bacteroides* spp. and *Parabacteroides* spp. after 8 weeks of vitamin D supplementation. It has been shown that *Bacteroides* and *Parabacteroides* were suppressed in patients with active inflammatory bowel diseases compared with normal controls (22, 23). Suppression of these two bacteria is believed to play a role in the pathogenesis of inflammatory bowel disease. The likely mechanism is that these bacteria help maintain the expansion of regulatory T cells, which, in turn, alleviate intestinal inflammation (24-26). This observation could therefore indicate another mechanism explaining the findings from clinical trials demonstrating an efficacy of vitamin D treatment in controlling the relapse rate in patients with inflammatory bowel diseases (27). In fact, the association between vitamin D status and *Bacteroides* and *Parabacteroides* is still inconclusive, since animal studies have reported inconsistent results (4, 28-31). One clinical trial did report an increase in the relative abundance of Parabacteroides in patients with Crohn's disease but not in healthy individuals during the third and fourth weeks of high dose oral vitamin D_3 supplementation (20,000 IUs per day for 3 days then every other day for 4 weeks) (10). Further studies are warranted to evaluate the association of vitamin D status with gut microbiota, and inflammatory bowel disease.

It should be acknowledged that our study has some limitations. Since this is a pilot study with a relatively small sample size, further studies with larger sample size should be conducted to confirm our findings. Furthermore, it might require a longer period of time to demonstrate a clinically significant and more robust change in the composition of gut microbiota in response to oral vitamin D supplementation. A study that evaluates both short-term and long-term effects of vitamin D on gut microbiota is required.

Conclusion

In conclusion, we observed that an increase in baseline serum 25(OH)D levels was correlated with increased bacteria associated with decreased risk of cardiovascular and metabolic diseases, obesity, and cancers. We also found that increased baseline 25(OH)D levels were inversely correlated with decreased periodondopathic bacteria. After 8 weeks of vitamin

D supplementation, we observed an alteration of gut microbiota towards a decrease in Firmicutes to Bacteroidetes ratio, which is an indicator associated with obesity and metabolic syndrome. Finally, we observed a dose-dependent increase in bacteria associated with decreased inflammatory bowel disease activity in response to various doses of vitamin D_3 supplementation.

Conflicts of Interest

Michael F. Holick is a consultant for Quest Diagnostics Inc. and Ontometrics Inc, and on the speaker's Bureau for Abbott Inc. The remaining Authors declare no conflict of interest regarding this study.

Authors' Contributions

Conceptualization: N. Charoenngam, A. Shirvani, T.K. Kalajian, M.F. Holick; Collecting data: T. Kalajian, A. Song; Data analysis: N. Charoenngam, A. Shirvani, A. Song; Writing - original draft: N. Charoenngam, A. Shirvani; Visualization: N. Charoenngam, A. Shirvani; Writing - review & editing: N. Charoenngam, A. Shirvani, M.F. Holick.

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