



Review Article

Impact of vegan diets on gut microbiota: An update on the clinical implications

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ABSTRACT

Numerous studies indicate that microbiota plays an important role in human health. Diet is a factor related to microbiota which also influences human health. The relationships between diet, microbiota, and human health are complex. This review focuses on the current literature on vegan diets and their unique impact on gut microbiota. We also report on the health benefits of a vegan diet for metabolic syndrome, cardiovascular disease, and rheumatoid arthritis concerning relevant impacts from gut microbiota. Despite evidence supporting the clinical relevance of vegan gut microbiota to human health, the whole mechanism awaits further investigation.

KEYWORDS: Diet, Microbiota, Vegan

INTRODUCTION

Gut microbiota is defined as microbes that collectively inhabit the gut ecosystem [1]. Several factors, including diet, age, birth mode, breast-feeding or formula-feeding, geography, exercise, alcohol consumption, and exposure to antibiotics may influence gut microbiota [2]. Among them, diet affects microbiota as well as human health [3,4].

Vegan diets, which are increasingly popular [5], have been associated with health benefits because they have higher amounts of fiber, folic acid, Vitamins C and E, potassium, magnesium, and many phytochemicals and more unsaturated fat than nonvegan diets [6]. Although some important nutrients such as protein, iron, and Vitamin B-12 are lacking [7-9], the vegan diet received the highest diet quality score measured by the Healthy Eating Index 2010 and the Mediterranean Diet Score in a recent study which included 1475 participants [10]. This review aims to clarify the relation between a vegan diet, gut microbiota, and clinical implications according to the current literature.

REVOLUTION IN MICROBIOTA ANALYSIS

Initially, fecal microbiota analysis was performed by culture. However, more than 60% of fecal bacteria cannot be

cultured. Thus, traditional culture-based approaches only partially represent the gut ecosystem [11,12]. Culture-independent molecular techniques targeted on 16S rRNA sequencing such as fluorescence *in situ* hybridization, denaturing gradient gel electrophoresis (DGGE), and quantitative polymerase chain reaction (qPCR) have been widely used in recent studies of fecal microbiota [13].

Several approaches have been developed to understand the potential functions of microbes. Metagenomics is a DNA-based technique to survey the genetic potential of microbial communities [14], whereas metatranscriptomics, metaproteomics, and metabolomics are techniques for understanding what the microbes do by detecting RNA, proteins, and metabolites [13].

MICROBIOTA FEATURES OF A VEGAN DIET

Studies usually compare the differences between vegan, lacto-ovo-vegetarian, and omnivorous diets. In 1987, van Faassen *et al.* [15] first compared a vegan diet with lacto-ovo-vegetarian and mixed Western diets for 20 days in


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12 men. They found that fecal lactobacilli and enterococci were the lowest in the vegan diet and fecal bile acids concentrations were also low in vegan and lacto-ovo-vegetarian diets. This was the first study that showed fecal flora compositions in a vegan diet differed according to the method of culture.

Recently, Zimmer *et al.* [16] conducted a large sample study which included 144 vegetarians, 105 vegans, and 249 omnivores as controls. Microbial counts (total colony-forming units) of four bacterial taxa, *Bacteroides* ($P = 0.001$), *Bifidobacterium* ($P = 0.002$), *Escherichia coli* ($P = 0.006$) and *Enterobacteriaceae* ($P = 0.008$), were significantly lower in the vegan group than the omnivore group. Furthermore, the study indicated that vegans consume more carbohydrates and fiber than omnivores. Stool pH was lower ($P = 0.001$) in vegans (pH = 6.3 ± 0.8) than omnivores (pH = 6.9 ± 0.8). Further, the acidic environment was not suitable for *E. coli* and *Enterobacteriaceae* growth. This may explain why *E. coli* and *Enterobacteriaceae* counts are low in vegans. Ferrocino *et al.* [12] used fecal microbiota analysis (bacterial culture and ribosomal RNA DGGE) in 153 healthy volunteers (51 vegans, 51 vegetarians, and 51 omnivores) and showed lower abundance (plate counts, $P < 0.05$ and band identification) of the *Bacteroides fragilis* group in vegans and vegetarians.

Many studies have focused on gut microbial profiles using molecular techniques based on 16S rRNA sequencing, including DGGE, qPCR, and pyrosequencing. In the study of Matijašić *et al.* [17] which included 20 vegans, 11 lacto-vegetarians and 29 omnivores, higher ratios (percentage of group-specific DNA in all bacterial DNA) of *Bacteroides-Prevotella* ($P < 0.01$), *Bacteroides thetaiotaomicron* ($P < 0.05$), *Clostridium clostridioforme* ($P < 0.05$), and *Faecalibacterium prausnitzii* ($P < 0.01$) were noted in vegetarians and vegans than omnivores. Similarly, a lower ratio of *Clostridium cluster XIVa* (relative difference: 0.03158 vs. 0.08108, $P = 0.004$) was noted in vegetarians and vegans in a

study of 32 lacto-vegetarians and 24 omnivores under quantified real-time PCR analysis of fecal 16S rRNA by Kaberdoss *et al.* [18] The study of Ruengsomwong *et al.* [11] in 36 vegans/vegetarians and 36 omnivores further indicated different abundance of potential pathogen varieties. The relative abundance of *Bilophila wadsworthia* (0.116 vs. 0.014, $P < 0.001$) and *E. hermannii* (4.703 vs. 0.716, $P = 0.032$) were higher in omnivores, whereas *Klebsiella pneumoniae* (2.170 vs. 0.793, $P = 0.032$) was higher in vegetarians and vegans. The detailed compositions of fecal microbiota influenced by geographical origin, age, gender, and body mass were heterogeneous within studies according to molecular technique [11,12,17]. However, the current literature indicates that the type of diet (vegan, vegetarian, and omnivorous) has an impact on fecal microbiota. Table 1 summarizes human gut microbiota as influenced by vegan, lacto-ovo-vegetarian, and omnivorous diets. Nevertheless, these results should be interpreted cautiously due to different methodologies for microbiota identification and varied sample sizes.

RELEVANCE OF VEGAN GUT MICROBIOTA ON HUMAN HEALTH AND DISEASES

Metabolic syndrome

Ley *et al.* [19] indicated that the ratio of Bacteroidetes and Firmicutes was related to obesity. In obese people, the relative proportion of Bacteroidetes was decreased, and Firmicutes was increased compared with that in thin people. After eating a reduced calorie diet, the proportion of Bacteroidetes to Firmicutes was increased with weight loss in obese people. Kim *et al.* [20] studied six obese people with type 2 diabetes and/or hypertension under a vegan diet for 1 month. Afterward, weight loss (average decrease $10.0\% \pm 2.4\%$), improved blood glucose levels, triglycerides, total cholesterol, low-density lipoprotein cholesterol, and hemoglobin A1c were noted. A reduced *Firmicutes-to-Bacteroidetes* ratio (decreased abundance of

Table 1: Effects of diet type on gut microbiota

	Vegan diet	Vegetarian diet	Omnivorous diet	Method (sample size)	Reference
<i>Lactobacillus</i>	↓			Culture (12)	[15]
<i>Enterococcus</i>	↓			Culture (12)	[15]
<i>Bacteroides</i>	↓			Culture (498)	[16]
<i>B. fragilis</i>	↓	↓		Culture and DGGE (153)	[12]
<i>Bacteroides thetaiotaomicron</i>	↑	↑		DGGE (60)	[17]
<i>Bacteroides/Prevotella</i>	↑	↑		DGGE (60)	[17]
<i>Bifidobacterium</i>	↓			Culture (498)	[16]
<i>E. coli</i>			↑	Pyrosequencing (72)	[11]
<i>E. coli</i>	↓			Culture (498)	[16]
<i>E. hermannii</i>			↑	Pyrosequencing (72)	[11]
<i>Enterobacteriaceae</i>	↓			Culture (498)	[16]
<i>C. clostridioforme</i>	↑	↑		DGGE (60)	[17]
<i>Clostridium cluster XIVa</i>	↓	↓		DGGE (60)	[17]
<i>Clostridium cluster XIVa</i>	↓	↓		qPCR (66)	[18]
<i>F. prausnitzii</i>	↑	↑		DGGE (60)	[17]
<i>Bilophila wadsworthia</i>			↑	Pyrosequencing (72)	[11]
<i>K. pneumoniae</i>	↑	↑		Pyrosequencing (72)	[11]

DGGE: Denaturing gradient gel electrophoresis, qPCR: Quantitative polymerase chain reaction, ↑: Relatively increased abundance, ↓: Relatively decreased abundance, *E. coli*: *Escherichia coli*, *E. hermannii*: *Escherichia hermannii*, *C. clostridioforme*: *Clostridium clostridioforme*, *F. prausnitzii*: *Faecalibacterium prausnitzii*, *K. pneumoniae*: *Klebsiella pneumoniae*, *B. fragilis*: *Bacteroides fragilis*, *B. thetaiotaomicron*: *Bacteroides thetaiotaomicron*

Firmicutes, $P = 0.052$; increased abundance of *Bacteroidetes*, $P < 0.05$) in the gut microbiota was also noted. This further indicates that a vegan diet leads to decreases in pathobionts such as the Enterobacteriaceae, similar to the study by Zimmer *et al.* [16]. It caused a reduced inflammation marker, fecal lipocalin-2, which is related to glucose tolerance and lipid metabolism. Kim *et al.* [20] showed the benefits of a vegan diet on the relationship between gut microbiota and metabolic syndrome.

Cardiovascular disease

Koeth *et al.* [21] indicated that a vegan diet reduces the risk of cardiovascular disease (CVD) by influencing gut microbiota. The mechanism is that intestinal microbiota metabolism of dietary L-carnitine, trimethylamine abundant in red meat, produces trimethylamine-N-oxide (TMAO). TMAO, one of the metabolites of the dietary lipid phosphatidylcholine, was shown to promote atherosclerosis [22]. Koeth *et al.* [21] compared 23 long-term (>1 year) vegans and vegetarians to 51 omnivores, and the fasting baseline TMAO levels were significantly lower ($P < 0.05$) in both the vegans and vegetarians. Even under oral carnitine challenge, the vegans and vegetarians had a reduced capacity to produce TMAO. Further analysis of fecal samples showed some bacterial genera differences in omnivores ($n = 30$) compared with vegans and vegetarians ($n = 23$) were related to plasma TMAO levels and the associated risk for atherosclerosis.

Rheumatoid arthritis

Peltonen *et al.* [23] included 53 rheumatoid arthritis (RA) patients who originally consumed an omnivorous diet. The study found significant changes in intestinal flora after patients shifted to a vegan diet for one year. Furthermore, fecal flora was different between patients with high improvement and low improvement. This indicates that gut profiles are associated with disease activity. Peltonen *et al.* [24] further studied 43 RA patients randomized into two groups consuming an uncooked vegan diet or omnivorous diet for 1 month. Significant changes in the fecal flora and decreased disease activity were noted in the vegan diet group, but not in the omnivorous diet group. This confirmed the connection between a vegan diet, fecal microbial flora, and disease activity in RA patients. Kjeldsen-Kragh [25] reported similar results from a controlled, single-blind trial with a vegan diet.

Parkinson's disease

Only one small group study has mentioned vegan diet and exercise benefits for patients with Parkinson's disease (PD) [26]. Scheperjans *et al.* [27] showed that the fecal *Prevotellaceae* in PD patients decreased 77.6% compared with that of healthy people. Furthermore, the increased relative abundance of fecal *Enterobacteriaceae* was associated with the severity of PD symptoms, including postural instability and gait difficulty. Keshavarzian *et al.* [28] showed a decreased relative abundance (average number of sequences) of fecal butyrate (short chain fatty acids)-producing bacteria from the genera *Blautia* (570 vs. 1032, $P = 0.03$), *Coproccoccus* (103 vs. 241, $P = 0.03$), and *Roseburia* (167 vs. 341, $P = 0.03$) in PD patients compared with healthy people. Dysbiotic microbiota may induce inflammatory responses

and influence PD through the enteric nervous system by alpha-synuclein pathology (also known as Lewy pathology) [29]. In one study, PD mouse model germ-free animals developed fewer plaques and almost no neurological deficits compared with conventionally colonized controls, and treatment of PD mice with antibiotics may result in improvement in neurological deficits [30]. Conversely, fecal transplantation from patients with PD to germ-free mice resulted in neurological deficits resembling PD [30]. However, therapeutic strategies such as types of diet on the modulation of the gut-brain axis of PD await further investigation.

Limitations of current studies

Although most current studies show that vegan or vegetarian diets influence fecal microbiota, there are several limitations in interpretation.

First, culture-independent molecular techniques, which have been used more often in recent studies, identify more microorganisms than conventional culturing techniques. Thus, the comparison between studies with different techniques is difficult.

Second, some studies only compared vegans with omnivores, others included vegans and vegetarians for comparison, and still, others compared vegans, vegetarian, and omnivores. Different study designs make interpretation controversial, especially with the role of a less-restrictive vegetarian diet.

Third, the durations of vegan diet intervention differ between studies and data on gut microbiota after continuing or discontinuing a vegan diet is lacking. Wu *et al.* [31] indicated that microbiome composition may change after a short-term diet, but alternative enterotype states are associated with a long-term diet. Further studies to clarify associations between the duration of a vegan diet and gut microbiota are warranted.

CONCLUSIONS

Vegan diets appear to affect gut microbiota as revealed by previous conventional culturing as well as recent culture-independent molecular studies. Furthermore, recent studies suggest that vegan diets may have various health benefits, including amelioration of metabolic syndrome, CVD, and RA [19-25].

Since there is tremendous progress in the revolution of microbiota technology, further studies are warranted to clarify the complex mechanisms and interrelationships between vegan diets and gut microbiota. More studies using culture-independent molecular techniques are needed, and databases will be constructed to identify "healthy" compositions of gut microbiota and how vegan diets alter gut microbiota. Moreover, using novel techniques with metagenomics, metatranscriptomics, metaproteomics, and metabolomics, more disease-specific genomes in gut microbiota will be explored to determine the impact of vegan diets. Hopefully, the opportunity applying such approach for precision medicine will come soon in the future.

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Conflicts of interest

The authors declare no conflicts of interest.

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