The gut microbiota’s role in diet-related cardiovascular health - an innocent bystander or a key mediator; the question remains

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Reduced meat consumption, especially of processed meat products, has been the center of focus in recent years due to increasing evidence for the association between meat consumption and health risks ¹,², with prospective cohorts indicating that higher consumption of total red meat and processed meat are associated with an increased risk of total and cardiovascular mortality ³. The gut microbiota, the actual bugs, and the gut microbiome, bugs and their genes, are subjected to changes throughout life, especially following diets. While short-term dietary changes may alter the gut microbiota diversity, these changes are not long-lasting ⁴. Yet, long-term and stable dietary regimens are thought to stabilize the individual’s microbiota profile ⁵.

Plant-based diets (PBDs) were demonstrated to affect the gut microbiota in different mechanisms linked to specific dietary components related to this eating pattern.

The role of the gut microbiota in the association between PBDs and CVD in humans is not fully addressed in randomized clinical trials (RCTs) settings. Few clinical trials examined the role of the gut microbiota while exploring the association between PBDs or PBDs components with CVD. Djekic D et al. performed a 4-week randomized crossover study on 150 patients with ischemic heart disease to examine the effect of a 4-week vegetarian diet (which differs from PBDs by being restrictive in animal protein rather than reducing animal protein) or a 4-week meat diet on cardiometabolic risk factors and gut microbiota ⁶. Along with a beneficial effect of the vegetarian diet over the meat diet in LCL-c, oxidized LDL-c, total cholesterol, and weight reductions, differences...
between these diets were observed in the relative abundance of several microbe
genera (of the *Ruminococcaceae* family, for example). Moreover, the baseline
composition of the gut microbiota was found to be associated with the response to diets
in the reduction of oxidized LDL-c. Rinott E et al. performed RCT among 294
abdominally obese or dyslipidemic adults that examined the effect of a 6-month
polyphenol-rich plant-based Mediterranean-style diet (green-Mediterranean diet) on
changes in CVD risk factors and CVD risk score. They suggested that the microbiome
taxonomic change mediates the diet-CVD risk score association. This trial also
suggested that change in *Bifidobacterium* abundance was inversely associated with
adherence to the green-Mediterranean diet. The reduction in *Bifidobacterium* and the
increase in genera from the *Ruminococcaceae* family were associated with a decrease
in Framingham risk score.

Examining specific plant-based components also suggested some microbiota
involvement in the association between plant-based foods and CVD. Klinder A et al.
suggested a dose X treatment interaction between increased intake of flavonoids and
gut microbiota. They found that among 122 healthy participants, LDL-c was inversely
correlated with some bacteria. A double-blind, placebo-controlled, parallel-designed by
Istas G et al. reported a correlation between changes in endothelial function and berry
polyphenols (mainly Flavonols and Hydroxycinnamic acids) and specific gut microbial
genera in 66 healthy adults. The authors suggested that the link between the
polyphenols in the berry, the gut microbiome, and the improved vascular function is
attributed to the ability of gut microbes to produce potentially bioactive phenolic
metabolites and short-chain fatty acids.
The review article by Kumar A et al. published in the European Journal of Preventive Cardiology highlighted four mechanisms of cardiovascular benefits of plant-based diets, mainly via the manipulations of plant-based diets on gut microbiota-host interactions. The authors have summarized the effect of PBDs on gut microbiota composition within different taxa levels. The authors also discussed four microbial metabolites products that may affect CVD risk factors: short-chain fatty acids, polyphenols, trimethylamine N-oxide, and bile acids. Other microbial metabolites resulting from aromatic amino acids (AAA) catabolism are also worth mentioning in this context. Phenylalanine, AAA in fish, milk, eggs, nuts, and beans, can be converted into phenylacetic acid via the gut microbiota. It is later transferred into phenylalanine-derived microbial metabolite phenylacetylglutamine in the liver. Other gut microbial-derived AAA metabolites are indoxyl sulfate and p-cresol sulfate from Tryptophan and tyrosine. The AAA metabolites may regulate immune, metabolic, and neuronal responses at local and distant sites. The altered gut microbial structure and metabolism are suspected to be linked with atherosclerosis in humans. There is a need for more studies confirming the involvement of the gut microbiota in the PBDs effect on CVD.

This review also provided a summary of current evidence and future insights on the effects of PBDs on CVD. The authors presented 17 methodological studies performed over the past three decades; half were RCTs examining the impact of vegetarian-style diets on known risk factors for CVD (blood lipids, glycemic markers, weight, etc.). Due to a small sample size within most of the trials reviewed, a meta-analysis might be appropriate in examining these associations. This review had not extended the discussion to potential factors that might influence the adherence and
susceptibility to PBDs and, therefore, differentially affect the gut microbiota and its association with CVD risk. For example, sex may influence adherence and susceptibility to the type of diet: biological differences between sexes may be further mediated by dissimilarities in adherence to diet patterns and nutrient metabolism, contributing to the differences in cardiovascular risk. Furthermore, there is evidence that sex differences may affect the CVD-gut microbiota link, due to differences in the gut microbiota composition between sexes and the bi-directional interaction between sex hormones and gut microbiota.

The diet-gut microbiota-CVD axis may be affected by the host genetic background. In genetically diverse mice that received either a high-fat-high-cholesterol or low-fat diet, gene X diet interactions were observed for a core group of cardiometabolic-related microbial taxa. In 1,264 individuals of the LifeLines-DEEP cohort, plasma CVD-related proteins were measured. The analysis showed that some genetic components mainly contributed to immune-related proteins, while the gut microbiome were mostly associated with proteins involved in metabolism and obesity-related inflammation. In addition, a joint genetic and microbial effect in CVD was observed, as some CVD-related proteins were associated with genetic factors and the gut microbiome. Significant gene X microbiome interactions were also observed for some of these proteins. Yet, CVD and related morbidities might result from more complex gene X diet X microbiome interactions. Thus, system-biology studies are needed to study these interactions further.

Adopting a PBD lifestyle may cause an inconsistent microbial response due to the individual composition of the gut microbiota and the duration of the consumed diet.
There is a need for more trials examining the role of the gut microbiota in the
association between PBDs and cardiovascular health to establish evidence-based
recommendations on a specific diet that may involve microbiota alterations related to
improved CVD health. Although some RCTs addressed gut microbiota changes
following PBDs interventions or specific plant-based foods and their effect on
cardiovascular health, it is still unclear whether the gut microbiota is a mediator,
confounder, or interacts with the diet and other exposures as genetic background to
affect cardiovascular health. The limitations in current evidence-based nutrition are due
to several factors: i. the lack of unified PBD given to participants and or different plant-
based components examined in different trials. Thus, the reproducibility and
generalizability of these trials and conclusions are limited. ii. difficulty in assessing
complex interactions in human studies. iii. report on different aspects of the gut
microbiota. Depending on the sequencing level, the report of the findings may be limited
to richness/composition, specific bacteria, or extended to metabolic pathways. iv. the
broad spectrum of CVD and CVD risk factors examined in these trials. v. duration of
PBDs lifestyle: whether short-term changes in the gut microbiota are sufficient to reduce
the long-term CVD risk or there is a need for adopting long-term stable habits to
stabilize the gut microbiome’s CVD protective effect is still to be determined.
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