ANNUAL REVIEWS

Annual Review of Medicine

A Crucial Role for Diet in the Relationship Between Gut Microbiota and Cardiometabolic Disease

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Annu. Rev. Med. 2020. 71:149–61

First published as a Review in Advance on September 3, 2019

The *Annual Review of Medicine* is online at med.annualreviews.org

https://doi.org/10.1146/annurev-med-062218-023720

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Keywords

gut microbiota, cardiometabolic disease, diet, dietary pattern

Abstract

Cardiometabolic disease (CMD), such as type 2 diabetes mellitus and cardiovascular disease, contributes significantly to morbidity and mortality on a global scale. The gut microbiota has emerged as a potential target to beneficially modulate CMD risk, possibly via dietary interventions. Dietary interventions have been shown to considerably alter gut microbiota composition and function. Moreover, several diet-derived microbial metabolites are able to modulate human metabolism and thereby alter CMD risk. Dietary interventions that affect gut microbiota composition and function are therefore a promising, novel, and cost-efficient method to reduce CMD risk. Studies suggest that fermentable carbohydrates can beneficially alter gut microbiota composition and function, whereas high animal protein and high fat intake negatively impact gut microbiota function and composition. This review focuses on the role of macronutrients (i.e., carbohydrate, protein, and fat) and

dietary patterns (e.g., vegetarian/vegan and Mediterranean diet) in gut microbiota composition and function in the context of CMD.

INTRODUCTION

Cardiometabolic disease (CMD) is an emerging term that mainly covers type 2 diabetes mellitus and cardiovascular disease. The term highlights the strong interrelation between these diseases. CMD is a typical consequence of (late stages of) the metabolic syndrome, a spectrum of clinical findings associated with increased CMD risk (1, 2).

CMD is a major contributor to morbidity and mortality worldwide. A recently published report by the World Health Organization (WHO) estimates that 31% of all global deaths are related to CMD (3). Optimization of existing and development of novel strategies to treat or prevent CMD are therefore highly warranted.

The multifactorial etiology of CMD makes early detection, prediction, prevention, and treatment notoriously complex. A fairly new player in the pathophysiology of CMD is the gut microbiota, which is often referred to as an additional organ, consisting of trillions of microbes living in a symbiotic state with their human host (4, 5). The gut microbiota has been shown to influence host metabolism and CMD development, for example by affecting the host immune system or by producing biologically active metabolites from dietary components (e.g., trimethylamine N-oxide from proteins or short-chain fatty acids from dietary fibers) (6–8). Multiple human cohort studies have shown that an imbalance in gut microbiota composition, in particular reduced number and diversity of bacterial genes, associates with development, and possible progression, of obesity and CMD (9–13). Indeed, obesity is characterized by a lower bacterial diversity and low microbial gene richness (9–11). Also, in overweight/moderate obesity, low microbial gene richness is associated with increased body mass index, as well as metabolic derangements including chronic low-grade inflammation and insulin resistance. Moreover, a decreased gut microbiota diversity is seen in 23–40% of overweight individuals and increases up to 75% in morbidly obese individuals (11). Additionally, human obesity is characterized by increased bacterial strains that display proinflammatory properties (9, 14).

Gut microbiota composition and function are regulated by several factors, such as diet, ethnicity, past or current medication use, smoking, and gender (14–18). Diet is one of the main shaping factors of the gut microbiota and can rapidly alter the gut microbiota, as exemplified by a short-term dietary intervention study (five days) in humans, which elicited drastic changes in gut microbiota composition (19). Moreover, several human studies have shown that dietary interventions can affect the gut microbiota composition and function and alter CMD risk, predominantly via production of microbially derived metabolites by the gut microbiota (8, 9, 20, 21).

It is well known that dietary interventions that promote weight loss can reduce CMD risk. Nevertheless, it is important to realize that most people are not able to maintain their reduced weight in the long term (22). Dietary interventions that alter gut microbiota composition and/or function provide a nonpharmacological method to prevent CMD or lower the burden on those already affected, making this form of dietary intervention perhaps a more durable method than traditional weight loss. However, multiple studies have shown a highly individual response to dietary interventions with regard to gut microbiota composition and/or function and subsequent CMD risk (23–26). These findings suggest that a personalized approach is necessary, where baseline gut microbiota composition predicts which individuals will benefit from a diet.

Studies that link diet, via the gut microbiota, to CMD risk/development are mostly associative in design. Importantly, fecal microbiota transplantation (FMT) studies in humans confirm rodent-derived evidence for causality between diet, gut microbiota, and CMD development (23, 27). However, designing nutritional studies in humans is a complex challenge, and it remains unclear what form of diet or dietary pattern is best suited to change the gut microbiota to improve host health in general or cardiometabolic health in particular. This review aims to provide insight into different dietary studies investigating the role of either specific macronutrients or dietary patterns that can influence CMD via the gut microbiota.

DESIGNING A DIETARY STUDY

There are several ways to design a nutritional intervention study. One approach is to focus on macronutrients (i.e., carbohydrate, dietary fat, and protein). This is also how current nutritional guidelines structure their recommendations on healthy food intake and how most studies investigating the effect of diet on the gut microbiota are performed (28, 29). This reductionist approach originates from a time when a majority of the population suffered from specific nutritional deficiencies (e.g., lack of vitamin C leading to scurvy) (30). Nevertheless, such an approach can be quite useful when deciphering the impact of specific macronutrients and performing hypothesis-generating experiments. One important drawback to these studies is the substitution effect: We unavoidably influence macronutrient composition when using isocaloric diets that focus on a specific macronutrient (31). For example, when comparing a high- versus low-protein diet, one is also comparing a low-carbohydrate/low-fat diet to a high-carbohydrate/high-fat diet.

It is important to take the potential confounding role of the substitution effect into account when interpreting results from dietary intervention studies aiming to affect a human phenotype via the gut microbiota. For example, studies that focus on the production of beneficial short-chain fatty acids (SCFAs) by the gut microbiota tend to focus on fiber intake as a dietary intervention. However, SCFAs can also be produced from amino acids (32). It is therefore crucial to take the intake of all macronutrients into account when interpreting the results of dietary intervention studies, especially with regard to the gut microbiota, as all macronutrients can affect the gut microbiota composition and function.

Another method to design nutritional studies is to focus on dietary patterns, such as a vegetarian or Mediterranean diet (33). Dietary pattern studies are informative, as they represent a more holistic approach to nutritional intake and are more easily maintained in an intervention setting. However, an important drawback is the difficulty of controlling for dietary intake (i.e., total composition of macronutrients) in such a design. Furthermore, the existence of multiple definitions of a dietary pattern complicates the comparability of these studies.

DIETARY STUDIES FOCUSING ON MACRONUTRIENTS

Carbohydrates

The role of carbohydrates in gut microbiota composition and function, and their subsequent effects on human cardiometabolic health, are the focus of most dietary intervention studies in the current literature (4, 34). Carbohydrates that are accessible to the gut microbiota, the vast majority of which resides in the colon, consist mainly of dietary fibers. These carbohydrates are resistant to breakdown by the digestive system of the host and are therefore not absorbed in the small intestine.

The breakdown of fibers and subsequent availability of fiber derivatives for the host depend on carbohydrate fermentation by the gut microbiota. An example of these derivatives are SCFAs,

which are key microbial metabolites (35, 36). The three major SCFAs produced by the gut microbiota are butyrate, propionate, and acetate. Several studies have shown that these SCFAs are beneficial in the context of CMD (8, 37, 38).

A randomized controlled clinical trial in subjects with type 2 diabetes mellitus showed the potency of a dietary intervention on the gut microbiota and CMD risk (8). In this study, the subjects who followed a high-fiber diet showed a significant decrease in hemoglobin A1c, lipid levels, and body weight compared to the control group. A high-fiber diet also led to increased butyrate levels by promoting the abundance and diversity of SCFA-producing bacterial strains. SCFAs are also described as playing beneficial roles in glucose homeostasis by increasing the production of the gut-derived glucose-regulatory hormone glucagon-like peptide-1 (GLP-1) and peptide YY, which enhances satiety (37, 39).

Interestingly, the overall gut microbiota richness decreased in the high-fiber group (8). Although this finding goes against the current dogma that high gut microbiota diversity is associated with improved clinical outcome in CMD, as was shown in a landmark study which found that a high microbial gene count was negatively associated with CMD (10), in this setting, not gut microbiota diversity but SCFA-producing strains appear to have a greater impact on reducing CMD risk.

To address causality, fecal samples of subjects with type 2 diabetes mellitus from both dietary groups were transplanted to germ-free mice (8). Mice that received FMT from the high-fiber group had lower fasting plasma glucose levels than mice that received a transplant from the control group. Importantly, the gut microbiota composition in receiving mice equaled the composition of the donors, further strengthening the notion that this process is gut microbiota driven. Adhering to fiber-rich diets can therefore be a simple method to increase SCFA levels and decrease CMD risk.

In line with this finding, barley β-glucans fiber-enriched bread (BGB) was shown to improve body weight, lipid levels, insulin resistance, and SCFA levels in subjects with (pre)metabolic syndrome, defined as having at least two of the five metabolic syndrome criteria (2, 40). Moreover, gut microbiota diversity and total cholesterol levels were decreased in the BGB-supplemented group compared to the control wheat bread group, without any significant changes to high-density lipoprotein (HDL) or low-density lipoprotein (LDL) cholesterol levels (40). In addition, circulating triglyceride levels were nonsignificantly lower in the BGB-supplemented group. This discrepancy between total cholesterol levels and LDL/triglyceride levels was likely a statistical power issue, as shown by a meta-analysis that studied the lipid-lowering effects of BGB, which showed a decrease in LDL cholesterol (41).

The study did report that the beneficial effects of BGB fiber supplementation were stronger in a subpopulation of subjects with a more severe form of metabolic syndrome (40). These findings imply that this dietary intervention might not be suitable for all subjects with (pre)metabolic syndrome, indicating a role for a personalized approach.

The notion of a personalized approach was also supported by a randomized crossover study in which 20 healthy individuals followed a dietary intervention for one week (42). The study compared industrial, low-fiber white bread with traditional whole-grain, high-fiber bread. Subjects in both groups showed high interpersonal differences in postprandial glycemic response (PPGR) to the different kinds of bread. Interestingly, a machine-learning approach revealed that the individual glycemic response to the bread could be predicted by baseline gut microbiota composition. The beneficial effects of fiber intake on CMD risk are dependent on the gut microbiota, likely via the formation of SCFAs. However, not all subjects respond equally well, and the next step is elucidating what mechanisms drive or inhibit the response.

Protein

Since the introduction of the Atkins diet, which advocates low carbohydrate but high protein and fat intake, protein diets have gained much attention. Nevertheless, the effects of protein diets on cardiometabolic health remain ambiguous (43). The breakthrough discovery of the protein-derived microbial metabolite trimethylamine (TMA), a precursor of trimethylamine N-oxide (TMAO), and TMAO's strong association with CMD risk, put protein and amino acid intake in the spotlight of microbiota/CMD research (7, 44).

A human intervention study has elucidated the pathway of TMAO synthesis and determined the contribution of an important intermediary step, which is the formation of γ-butyrobetaine (γBB) (45). The authors showed that the gut microbiota catabolizes dietary L-carnitine (found mainly in red meat) to γBB, which is an intermediary product for the formation of TMA. TMA is then converted to TMAO by hepatic flavin-containing monooxygenase 3 (FMO-3). This process was shown to be markedly disturbed upon antibiotic treatment, indicating that the pathway is gut microbiota dependent.

Recently, the gut microbiota–produced metabolite imidazole propionate (ImP) was associated with insulin resistance (46). The gut microbiota of type 2 diabetes mellitus patients was shown to produce more ImP from the essential amino acid histidine (mainly found in protein-rich food, such as tuna) than the gut microbiota of healthy individuals. This finding further indicates that the gut microbiota, at least in part, contributes to CMD risk via translation of dietary cues. Mechanistically, ImP was shown to increase insulin resistance by activating the mechanistic target of rapamycin complex 1 (mTORC-1), which increased serine phosphorylation and subsequent degradation of insulin receptor substrate (IRS).

The effects of dietary amino acids on gut microbiota composition and function have been mainly studied in animal models. For instance, intermittent deprivation of leucine, an essential branched-chain amino acid, was shown to improve insulin resistance in a genetic mouse model of diabetes mellitus (47). Of note is that these mice did not display significant weight changes but did have higher proliferation rates of β cells in the pancreatic islets. Furthermore, the gut microbiota was also altered, as particularly exemplified by an increased Bacteroidetes/Firmicutes ratio, which correlated with improved fasting blood glucose levels.

The metabolism of tryptophan, another essential amino acid, by the gut microbiota was shown to play an important role in intestinal inflammation and barrier function (48, 49). Intestinal inflammation can increase CMD risk by increasing production of bacterial lipopolysaccharides (LPSs). LPSs can migrate into the systemic circulation and induce a state of endotoxemia, which increases insulin resistance and triggers weight gain (50). The proposed mechanism of LPS migration into the systemic circulation is by means of increased gut permeability. Indeed, a human study showed that gut permeability is increased in subjects with type 2 diabetes mellitus compared to healthy controls and that this increase positively correlates with markers of systemic inflammation and CMD risk (44).

The role of dietary protein and amino acids is gaining more attention; the field's focus appears to be switching from the effects of fibers to the effects of protein on gut microbiota composition and function, and thereby on human metabolism. Gut microbiota–derived metabolites are an especially interesting area of research, since they represent functional and potentially targetable products of the gut microbiota (51, 52).

Dietary Fat

Dietary fat has long been associated with increased CMD risk. Although recent large cohort studies have shown data contradicting these associations (53, 54), dietary studies have reproducibly

shown that fat changes the composition of the gut microbiota and thereby possibly influences CMD (55, 56).

In a randomized controlled dietary intervention study, subjects with extreme metabolic syndrome (i.e., scoring 5 out of 5 metabolic syndrome criteria) followed a low-fat diet for two years (55). Simultaneously, a group of obese subjects without metabolic syndrome and a healthy control group followed an identical diet. Gut microbiota dysbiosis (i.e., microbial imbalance) was observed at baseline in the metabolic syndrome group compared to the obese and healthy control groups. Interestingly, gut microbiota dysbiosis was partly reversed in the metabolic syndrome group following the low-fat diet, showing a microbiota composition similar to those of the obese and control groups. The microbiota of the latter two groups remained relatively unaffected from baseline. Although the study comprised only male subjects and adherence to diet was deduced from questionnaires instead of food diaries, these observations imply that a low-fat diet can beneficially affect the gut microbiota composition and CMD risk in subjects with extreme metabolic syndrome.

A high-fat diet can increase CMD risk via the gut microbiota. This was shown in a mouse study where the gut commensal *Bilophila wadsworthia*, a microbe associated with local inflammation, was increased after a high-fat diet (57). *B. wadsworthia* was shown to influence bile acid composition, resulting in more primary bile acid conjugates and a higher total level of bile acids. This is important because bile acids have critical properties for fat absorption and also function as signaling factors in human metabolism (58).

The immune system has long been recognized to play an important part in the development of CMD, as has been comprehensively reviewed elsewhere (59, 60). The gut microbiota has been shown to directly influence the host immune system after dietary fat intake, as was shown in a rat study (61). A high-fat diet modulated the intestinal immune system by decreasing Treg cells and increasing Th1 cells, leading to a state of chronic inflammation (61, 62). A high-fat diet can also increase gut permeability, giving rise to an increased circulating level of LPSs, which results in low-grade inflammation and is associated with weight gain and type 2 diabetes mellitus progression (63, 64).

In addition to deleterious effects, such as increased inflammation and altered bile acid signaling via gut microbiota changes, dietary fat can have positive effects via medium-chain triglycerides (MCTs) (64). MCTs are smaller than long-chain triglycerides and are digested faster. MCTs are largely transported to the liver via the portal vein after digestion and are minimally transported via chylomicrons through the lymphatic system. Several studies have shown that MCTs can influence the gut microbiota by preventing LPS-induced endotoxemia and by antimicrobial effects on potentially harmful microbes (65, 66). Furthermore, a meta-analysis showed that increased dietary intake of MCTs (found in coconut oil, palm kernel oil, and bovine milk) can reduce CMD risk by reducing body fat and weight; however, the meta-analysis did not take the role of the gut microbiota into account (67).

In general, high-fat diets appear to have a negative effect on gut microbiota composition and function, leading to an increased CMD risk. However, an important nuance is the source of dietary fat, as MCTs have been reported to beneficially influence the gut microbiota. Future research should focus on disentangling the effects of different fat sources on gut microbiota composition and function.

DIETARY STUDIES USING DIETARY PATTERNS

Vegetarian and Vegan Diets

Vegetarian and vegan diets have become increasingly popular in industrialized society, likely due to multiple favorable health outcomes associated with these diets (68, 69). A vegetarian diet is

generally defined as a dietary pattern that excludes meat and meat products, whereas a vegan diet is defined as abstinence from all animal-derived substances. A recent meta-analysis has shown that both vegetarian and vegan diets lead to lower all-cause mortality and lower CMD risk (68). However, it is important to note that very few randomized controlled trials have been conducted where the distinction between vegetarian and vegan dietary composition was clearly defined. Furthermore, nutritional deficiencies have been associated with these diets, and supplementation of specific nutrients is advised (70).

Multiple studies have shown that vegan and vegetarian diets influence gut microbiota composition (71–73). The gut microbiota composition of children from a western European country, with a western omnivorous diet, was compared to the gut microbiota composition of children from a rural African village, where the diet was mainly vegetarian (71). The gut microbiota composition of these groups was highly distinct, with a greater diversity in the gut microbiota of rural African children. Furthermore, the children from the rural African village had higher levels of fecal SCFAs. Both factors are associated with reduced CMD risk (9, 35).

As described above, lower TMAO levels have been associated with lower CMD risk. The gut microbiota of vegans/vegetarians produces markedly less TMA, and subsequently less TMAO, from γBB, and this contributes to a lower CMD risk (45). Although it was speculated that the gut microbiota from vegan/vegetarian individuals simply lacks the bacterial strains to convert γBB to TMA, this was not directly determined in the study.

In contrast, a recently published double-blind randomized controlled trial did not show effects of vegan microbiota composition on TMAO production. In this trial, FMT from vegan donors to recipients with metabolic syndrome did change recipients' gut microbiota composition toward the donor composition, but failed to elicit a response in TMAO levels (72). An explanation for this finding could be that a single vegan FMT is insufficient to induce functional changes in TMAO production.

Nevertheless, the gut microbiota likely plays a crucial part in mediating the beneficial effects of a vegetarian/vegan diet to reduce CMD risk. Mechanistically, these diets raise levels of SCFAs and lower TMAO, since fiber intake is increased and animal protein intake is decreased. Low SCFAs and high TMAO have been implicated in CMD development (36, 45). Furthermore, these diets comprise plant protein, which has been associated with reduced CMD risk, rather than animal protein (74).

Mediterranean Diet

The Mediterranean dietary pattern is characterized by low intake of meat and high intake of fruit, vegetables, legumes, and olives (75). The diet has been associated with reduced CMD and mortality (75, 76). One study found that Greek-born Australians showed lower mortality rate and lower CMD than the general Australian population, despite a higher prevalence of risk factors for CMD, such as obesity, dyslipidemia, and hypertension (77). This paradox can possibly be explained by the gut microbiota composition and formed metabolites, as the Mediterranean diet comprises high fiber and low animal protein intake. As mentioned above, this likely increases production of beneficial SCFAs and lowers production of TMAO, which is associated with higher CMD risk.

Interestingly, a Mediterranean diet did not lead to differences in gut microbiota diversity in a human observational study (78). However, the diet did lead to higher levels of SCFA-producing bacteria and consequently higher fecal SCFA levels, which have been associated with a decrease in CMD risk. Moreover, the subjects who adhered poorly to a Mediterranean diet had higher levels of urinary TMAO, which is associated with an increased CMD risk.

The finding that a Mediterranean diet did not influence gut microbiota diversity was surprising but was independently reproduced by a human intervention study (55). This study, discussed above with regard to dietary fat, compared three groups: subjects with severe metabolic syndrome, obese subjects without metabolic syndrome, and healthy controls. All subjects followed a Mediterranean diet for two years. The authors did not find a discrepancy between gut microbiota diversity among these groups. Moreover, no differences were observed between the gut microbiota compositions of the two groups without metabolic syndrome. However, as mentioned, the gut microbiota composition of subjects with metabolic syndrome differed from the other two groups at baseline, and two years of a Mediterranean diet altered the composition to mimic the non–metabolic syndrome groups.

Although a Mediterranean diet has been associated with reduced mortality and CMD risk, it remains difficult to assess the role of the gut microbiota. To date, no FMTs have been done using donors who followed a Mediterranean diet. Furthermore, a clear definition of a Mediterranean diet is lacking, which makes comparisons between studies difficult.

SUMMARY AND FUTURE PERSPECTIVES

The gut microbiota has emerged as a pivotal player in the development of CMD, such as type 2 diabetes mellitus and cardiovascular disease. Dietary interventions can influence gut microbiota composition and function and therefore affect CMD risk (79). An overview of how diet can influence CMD risk via the gut microbiota is depicted in **Figure 1**. In general, fermentable carbohydrates have been shown to reduce CMD risk via microbial production of SCFAs. Animal protein has been shown to increase CMD risk by increasing production of microbial metabolites such as TMAO and ImP. High fat intake can increase CMD risk by promoting systemic inflammation through increased endotoxemia and gut permeability.

However, it is important to note that studies performed to date mainly used 16S RNA techniques to decipher the gut microbiota composition. The 16S RNA technique, in contrast to metagenome sequencing, is restricted in its resolution and is not able to look at functionality or species level of the gut microbiota in detail (80). The next step in elucidating the effects of dietary intervention on gut microbiota composition and function and subsequent CMD risk is designing human intervention studies focusing on gut metagenome sequencing and metabolite production in relevant human CMD models.

Nutritional studies focusing on the role of gut microbiota composition and function in CMD risk are complicated by the fact that the individual response to dietary interventions is highly variable (9, 13, 77, 78). It is still unclear what distinguishes these so-called responders and nonresponders. Host characteristics, such as baseline microbiota composition, might underlie these response discrepancies. In addition, particular features of the intervention (FMT, mucosal adherence of probiotics, or dietary interventions) (23, 81–83) may alter gut microbiota response and susceptibility to the intervention. For example, the effect of FMT in altering recipients' gut microbiota composition and function might be influenced by donor gut microbiota diversity (84).

These studies imply that a "one size fits all" solution for use of dietary interventions to target gut microbiota composition/function and affect CMD risk does not exist. Rather, the future is in personalized approaches and taking baseline microbiota composition of subjects into account in order to enhance efficacy of intervention.

One landmark study in which the concept of a personalized approach was introduced in humans showed a high variability in PPGR to similar meals. The PPGR correlated with gut microbiota composition. The authors then devised a machine-learning approach where the PPGR could be predicted per individual by taking gut microbiota composition into account (25). This

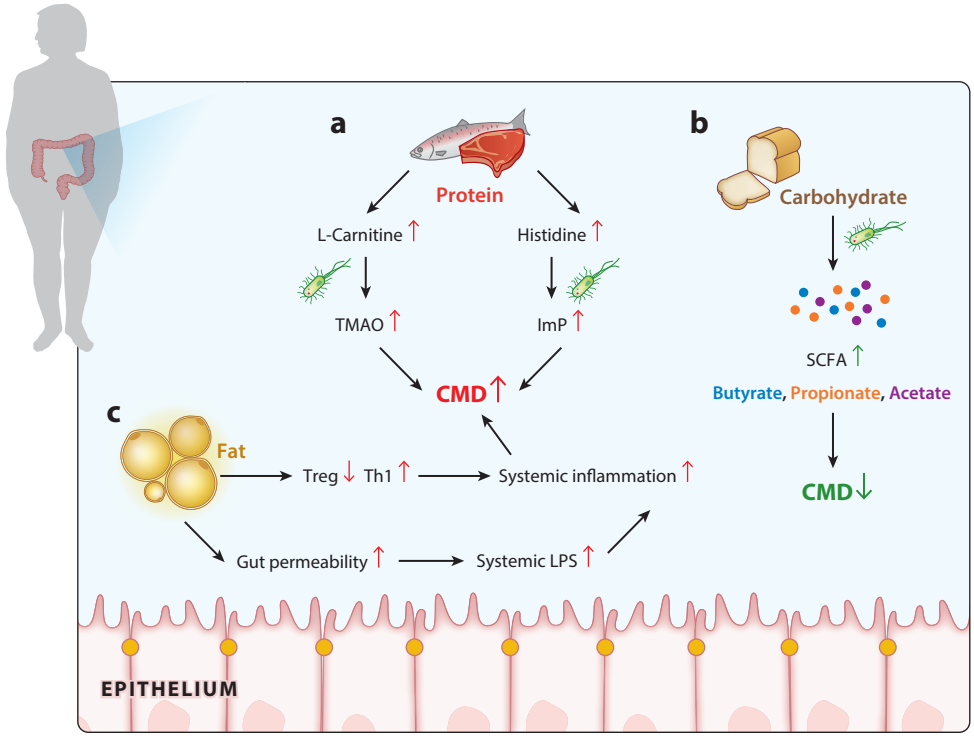

Figure 1

Macronutrients affect cardiometabolic disease (CMD) risk via modulation of the gut microbiota. The three macronutrients (i.e., carbohydrate, protein, and fat) alter gut microbiota composition and/or function, thereby affecting CMD risk. The following pathways are the best studied, but others likely exist. (*a*) Dietary animal proteins that contain L-carnitine or histidine are converted by the gut microbiota to eventually yield trimethylamine N-oxide (TMAO) and imidazole propionate (ImP), respectively. These metabolites have been shown to increase CMD risk. (*b*) Microbiota-accessible carbohydrates (mainly fiber) can be metabolized by the gut microbiota to yield beneficial short-chain fatty acids (SCFAs) butyrate, propionate and acetate, which have been shown to reduce CMD risk. (*c*) Dietary fat leads to increased systemic low-grade inflammation, a well-recognized risk factor for CMD, by increasing gut permeability. Increased gut permeability enhances passage of the bacterial wall component lipopolysaccharide (LPS), which has been shown to increase systemic inflammation and alter the gut mucosal immune response. Dietary patterns (e.g., vegetarian/vegan, Mediterranean diet) are characterized by preferential intake of specific macronutrient(s) and will therefore follow the same pathways as described above with regard to gut microbiota modulation and altered CMD risk.

personalized approach paved the way for upcoming use of machine-learning approaches that take into account individual gut microbiota data to effectively construct personalized dietary interventions to lower CMD risk.

Similarly, mucosal adherence of a probiotic with presumed effects on CMD health was shown to be highly variable, adhering to the gut mucosa of some but not all human subjects; the responders and nonresponders could be predicted on the basis of individual host and microbiota features (83). The developed algorithm can be used to predict which individuals may experience beneficial effects of probiotic use. Nevertheless, it is important to recognize that these algorithms have been developed with data on healthy volunteers from a fixed ethnic and geographic group. Health status, ethnicity, and geography can all influence the gut microbiota composition (15, 85). Therefore,

multiple independent studies are needed worldwide, in groups of different ethnic background and disease status, to create an algorithm that can take these crucial factors into account. Only then can we achieve a personalized approach to reducing CMD by developing dietary strategies that affect gut microbiota composition and function.

DISCLOSURE STATEMENT

M. Nieuwdorp is on the Scientific Advisory Board of Caelus Pharmaceuticals.

ACKNOWLEDGMENTS

I. Attaye is supported by a JPI MICRODIET Grant (5290510105). M. Nieuwdorp is supported by a ZONMW-VIDI grant 2013 (016.146.327) and a Le Ducq consortium grant (17CVD01).

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