REVIEW FROM ASN EB 2015 SYMPOSIUM

Postprandial Metabolism of Macronutrients and Cardiometabolic Risk: Recent Developments, Emerging Concepts, and Future Directions[1,2]

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death in the United States. Although the role of habitual lifestyle factors such as physical activity and dietary patterns in increasing CVD risk has long been appreciated, less is known about how acute daily activities may cumulatively contribute to long-term disease risk. Here, the term acute refers to metabolic responses occurring in a short period of time after eating, and the goal of this article is to review recently identified stressors that can occur after meals and during the sleep-wake cycle to affect macronutrient metabolism. It is hypothesized that these events, when repeated on a regular basis, contribute to the observed long-term behavioral risks identified in population studies. In this regard, developments in research methods have supported key advancements in 3 fields of macronutrient metabolism. The first of these research areas is the focus on the immediate postmeal metabolism, spanning from early intestinal adsorptive events to the impact of incretin hormones on these events. The second topic is a focus on the importance of meal components on postprandial vasculature function. Finally, some of the most exciting advances are being made in understanding dysregulation in metabolism early in the day, due to insufficient sleep, that may affect subsequent processing of nutrients throughout the day. Key future research questions are highlighted which will lead to a better understanding of the relations between nocturnal, basal (fasting), and early postmeal events, and aid in the development of optimal sleep and targeted dietary patterns to reduce cardiometabolic risk. *Adv Nutr* 2016;7:364–74.

Keywords: meal metabolism, incretins, lipids, postprandial, vascular function, sleep restriction

Introduction

Cardiovascular disease (CVD)[9] is the leading cause of deaths in the United States, accounting for ~830,000 deaths annually (1). Obesity and insulin resistance are predisposing factors for CVD and type 2 diabetes, and much has been learned about the effects of lifestyle patterns that contribute to dysfunctional macronutrient metabolism. Epidemiologic findings provide clear support that patterns of behavior extending over years contribute to disease risk (2), and it is well recognized that the daily accumulation of metabolic events eventually disrupts metabolic homeostasis. In particular, accumulating evidence supports the critical role of acute postprandial responses to incrementally contribute to CVD risk (3), with postprandial hyperglycemia as an example; it better predicts CVD-related deaths compared with fasting glucose concentrations, regardless of the presence of diabetes (4). Because short-term metabolic events precede overt disease, examining metabolic stressors throughout the 24-h, sleep-wake-eating cycle may uncover disease risk that may be otherwise hidden while providing a basis for targeted strategies to mitigate this risk.

Recent advances in 3 distinct fields of macronutrient metabolism have resulted in the identification of key mediators

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[9] Abbreviations used: ADMA, asymmetric dimethylarginine; CEHC, carboxyethyl-hydroxychromanol; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eNOS, endothelial nitric oxide synthase; FMD, flow-mediated dilation; GLP, glucagon-like peptide; GTT, glucose tolerance test.

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that regulate the physiologic processing of meal nutrients and the manner in which short-term metabolic effects contribute to disease. Specifically, this review focuses first on discussing disease-associated alterations in the normal pathways of nutrient absorption and assimilation. Recent work has produced surprising discoveries of new pathways that control intestinal lipid processing and the role of incretins to regulate lipid absorption (5). A second area described here includes studies that link food processing to cardiometabolic disease risk by focusing on metabolic events that occur once food has been absorbed. Clinical and preclinical studies have uncovered mechanisms by which elevated postprandial concentrations of nutrients (e.g., glucose) promote vascular dysfunction through oxidative stress-related pathways (6). This research holds much promise to explain how meal metabolism, when repeated daily throughout a lifetime, contributes to the long-term development of cardiometabolic disease. A third focus of this review poses the question of whether metabolic events that occur in humans as they become fasted during the early hours of the morning (0200–0600) are influenced by sleep restriction. In addition discussed here is whether these events in the sleep-deprived state may also feed forward to impair subsequent nutrient handling throughout the day. This area has been one of active focus (7), as has the study of sleep restriction's impact on diabetes and obesity risk (8, 9). The collective advances of these distinct, but complementary, research areas are supported by the use of stable isotopes and kinetic measurements such as insulin clamps and intravenous glucose tolerance tests (GTTs), meal-feeding paradigms to measure metabolic responses over time in nonsteady states, the development of pharmaceutical compounds to specifically target the action of gut hormones, the improvement of technical approaches to assess endothelial function in vivo (10), and the development of new technologies that include the expansion of clinical research units to test sleep disorders. As metabolic research advances, it is likely that discoveries yet to come will underscore the interplay between acute stressors and macronutrient metabolism. Accordingly, we also highlight key unanswered scientific questions that are expected to serve as the focus of future research.

Enterocyte Lipid Handling

The complexity of dietary fat absorption. Measurements of the timing of carbohydrate absorption have shown that ~75 g is completely absorbed within 3 h after the start of the meal (11). By contrast, to completely absorb a roughly equivalent caloric load of fat (40 g) may take up to 18 h of transit through the enterocyte. During this complex process, dietary FAs are resynthesized into TGs and packaged into apoB48-containing chylomicrons, before entering the blood through the thoracic duct of the heart (**Figure 1**) (12). Chylomicrons are secreted in both the fasting and fed states (13). In the fasting state, chylomicrons are smaller, ~10,000 TGs/particle (14), whereas those secreted after meals can carry ~50,000–100,000 TG molecules/particle (15). Thus, meal feeding increases the number of apoB48 particles secreted from the intestine to a smaller extent than it increases the number of TGs carried/particle (16).

It is now recognized that at the onset of meal consumption, chylomicrons are immediately released that carry lipid previously stored within an enterocyte lipid pool (17, 18). Such cephalic phase lipid mobilization can occur *1*) at the onset of eating a standard mixed meal (containing protein, carbohydrate, and fat); *2*) after drinking a glucose solution (19); *3*) while masticating, tasting, and expectorating (sham feeding) a whole food such as pizza (20); and *4*) during sham feeding with a more simple stimulus such as cream cheese, which resulted in mobilization of a prestored, enterocyte lipid pool within 3 min (17). Further, in healthy individuals, chylomicrons are released, and a previous meal's lipid can be detected in plasma if the cephalic phase stimulus occurs even 18 h after the last meal (17). The physiologic advantage or consequences of enterocyte lipid stores are unknown, but Parks and colleagues hypothesize that stores function to support constitutive chylomicron formation and secretion at a low rate in the fasting state and that this allows for a rapid ramping up of TG handling after large quantities of dietary fat are consumed in a high-fat meal. Furthermore, given that food consumption increases the release of intestinal hormones such as glucagon-like peptide 1 (GLP)-1 and GLP-2 and glucose-dependent insulinotropic peptide, early postprandial release of these incretins may provide a feed-forward signal to the periphery to increase fat storage (Figure 1). For instance, glucose-dependent insulinotropic peptide promotes FA esterification and adipocyte differentiation (21–23). In this way, early cephalic events may connect the size of the dietary lipid load with lipid secretion and body storage.

What constitutes a fatty intestine? With the use of a stable isotope of TGs (deuterated tripalmitin) added to an evening meal, Chavez-Jauregui et al. (17) demonstrated that chylomicrons secreted the next morning in the fasted state carried the evening meal label. As shown in **Figure 2**, those subjects with the highest quantities of body fat exhibited the lowest enrichments of the label in the fasting state and also early in the postprandial process (within 1 h after food consumption). A greater dilution of the dietary label as it passed through the intestine suggested that subjects with greater body fat had greater quantities of stored lipid in the intestine. Interestingly, subjects performed this study of sham-feeding twice (either low-fat or high-fat cream cheese), and the observation was reproducible, suggesting that intestinal lipid stores are an individual characteristic of subjects. The metabolic syndrome shown to be associated with excess TGs stored in the liver and other ectopic sites (muscle, heart), and the data shown in Figure 2 suggest that being overweight may also be associated with excess lipid stored in the intestine.

Robertson et al. (19) have performed intestinal biopsies in subjects after consumption of a meal fat challenge, and electron micrographs of duodenal tissue provide direct evidence of large amounts of lipid stored intracellularly. Exploration

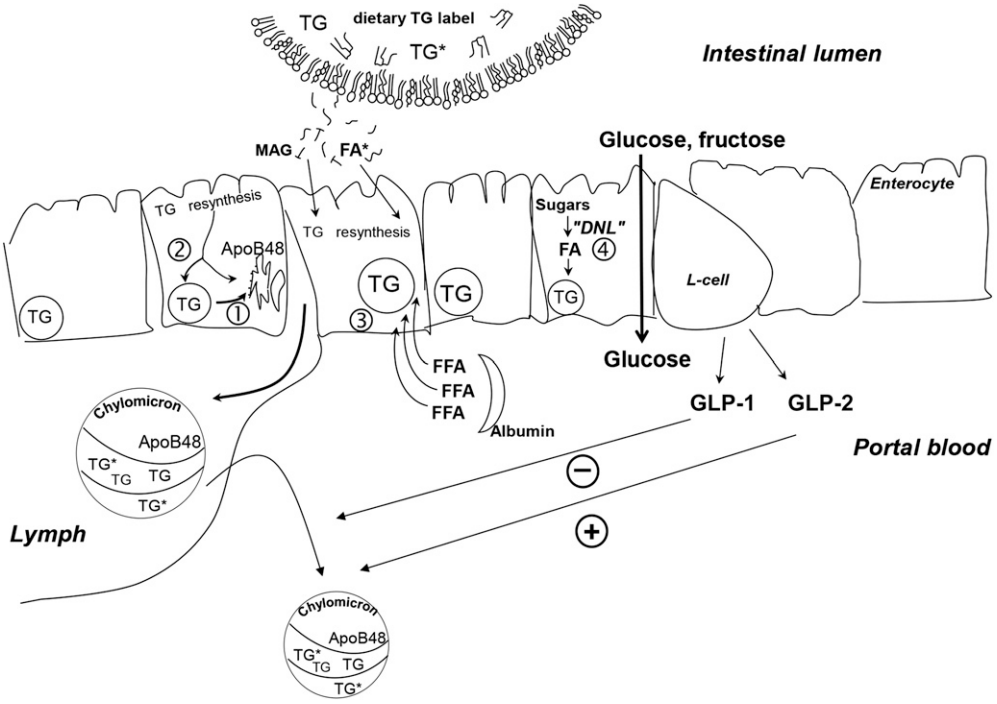

FIGURE 1 Metabolic processes that support intestinal lipid absorption, chylomicron synthesis, and the role of GLP-1 and GLP-2 in glucose and lipid absorption. Numbered pathways depict *1*) use of stored enterocyte TGs for chylomicron synthesis, *2*) mixing of newly absorbed TGs into the stored lipid pool and direct use for chylomicron TG synthesis, *3*) use of the plasma FFA pool for chylomicron TG synthesis, and *4*) the potential for newly made FAs from dietary carbohydrates through the process of de novo lipogenesis. GLP-1 decreases chylomicron production (-). GLP-2 stimulates (+) the release of stored, preformed chylomicrons into the circulation. DNL, de novo lipogenesis; GLP, glucagon-like peptide; MAG, monoacylglycerol.

of this process by taking intestinal biopsies is impractical in most human clinical studies. One potential method to estimate the size of intestinal lipid stores in humans in vivo is to use a combination of TG-labeled meals, analysis of plasma TGs by mass spectrometry, and calculation of the intracellular precursor FA pool enrichments with the use of a method called mass isotopomer distribution analysis (24). Such studies are currently under way to test the impact of subject body fat on enterocyte lipid handling.

Although stored intestinal lipid is used to support chylomicron-TG secretion early in the postprandial period, it may take up to 4 h after a meal for chylomicron lipid to begin to reflect the composition of the meal-TG FAs. One other source of FAs that can be used to support chylomicron-TG synthesis is the plasma FFA pool. Indirect data support the potential uptake and esterification of plasma FFAs through the basolateral membrane of the enterocyte (designated as pathway 3 in Figure 1). Lewis and colleagues (25) have infused intralipid and heparin to increase the plasma concentration of FFAs and found that apoB48 secretion was increased ~66%. Physiologic states associated with adipose insulin resistance (e.g., sleep restriction, obesity), which also cause higher plasma FFA concentrations, may also be associated with higher fasting apoB48 concentrations (26). Direct evidence for enterocyte FFA uptake has yet to be generated by labeling plasma FFAs and detecting this label directly in TGs carried in newly secreted chylomicrons. One barrier to such studies is the lack of efficient methods to separate chylomicrons from VLDL, and this remains a key limitation for human studies in this field. Studies in rodents can circumvent this limitation by collecting lymphatic output in the fed state to assess apoB48 secretion (27). Thus, rodent models could be used to directly test the contribution of the plasma FFA pool to enterocyte chylomicron-TG synthesis.

A final source of FAs used for enterocyte TG synthesis is the process of de novo lipogenesis (Figure 1, pathway 4). Recently, Veilleux et al. (28) investigated de novo lipogenesis in intestinal tissue explants obtained from patients undergoing bariatric surgery. The tissue from subjects categorized as insulin resistant (HOMA-IR) had elevated rates of lipogenesis ex vivo as determined by the incorporation of ^{13}C-acetate into lipids. Esterification of oleic acid into cellular lipids was also evident in secreted lipoproteins ex vivo. However, whether the intestinal lipogenic pathway can contribute to intestinal lipid storage and/or secretion during carbohydrate overfeeding in vivo in humans is unknown. Indirect evidence for this mechanism is supported by a recent study in healthy individuals (29) in which intraduodenal co-infusion of either glucose or fructose with a lipid emulsion resulted in increased production rates of apoB48 compared with co-infusion of the lipid emulsion and saline (6.0-fold and 1.6-fold, respectively). However, the investigators have proposed that this effect of sugars on chylomicron production may be a result of a shift of intracellular lipid from storage to the assembly pathway and that this is likely enhanced in response to hyperglycemia (30).

The Influence of Intestinal Hormones on apoB48 Synthesis

In addition to the sources of lipid used for chylomicron synthesis, some studies have uncovered the role of hormones in

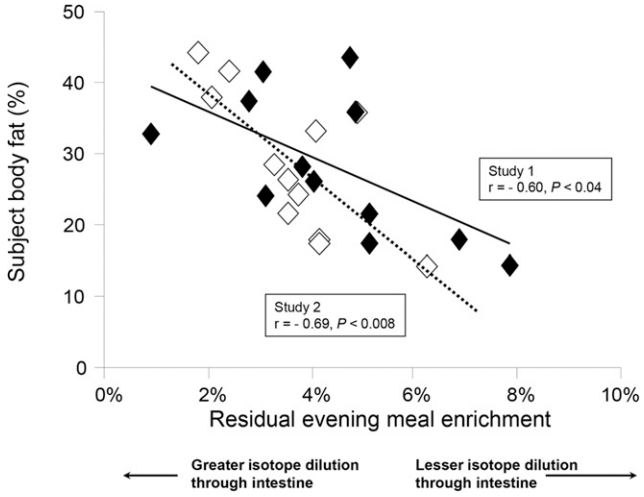

FIGURE 2 Relation between subject body and dilution of dietary fat isotope through the intestine. On 2 occasions, 12 healthy men and women consumed 2 g of $^{13}C_2$ triolein with a standardized evening meal (34% fat, 57% carbohydrates). The next morning, chylomicrons were isolated in the fasting state, and TGs were analyzed for the presence of the label that originated from the evening meal. Body fat was measured by DXA. Open diamonds represent the data from the first study (sham feeding with low-fat cream cheese), and filled diamonds represent data from the second study (sham feeding with high-fat cream cheese). Adapted from reference 17 with permission.

the control of apoB48 particle secretion. Lewis and colleagues (25) have demonstrated that insulin acutely inhibits apoB48 secretion in healthy humans (in part related to suppression of plasma FFAs), but this suppressive effect of insulin is blunted in individuals with type 2 diabetes (31). Thus, these studies provided the first evidence in humans that intestinal insulin resistance may underlie the overproduction of chylomicrons observed during these conditions. Most recently, studies have provided new insight into how gut hormones regulate chylomicron secretion. The intestinally derived peptides GLP-1 and GLP-2 are secreted by intestinal L cells in response to nutrient ingestion (Figure 1), particularly carbohydrates and fat (32, 33). Both peptides are degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), although to a different extent with GLP-1 having a shorter half-life in the circulation (~1.5 min) than GLP-2 (~7 min), as reviewed by Holst et al. (34). Importantly, GLP-1 and GLP-2 were shown to exert opposing effects on regulating chylomicron secretion.

GLP-1 reduces chylomicron secretion. The clinical use of incretin-based therapies (GLP-1 receptor agonists and DPP-4 inhibitors) in type 2 diabetes suggests a role for these agents in ameliorating fasting and postprandial hyperlipidemia. This emerging evidence was discussed comprehensively in a recent review that poses gut hormones as key regulators of intestinal-derived lipoprotein secretion (5); thus, this topic will not be further elaborated here. Of note, mechanistic studies in healthy humans have shown that exenatide (GLP-1 receptor agonist) and sitagliptin (DPP-4 inhibitor) can reduce intestinal, but not hepatic, lipoprotein production acutely, independent of glycemic status and weight loss (35, 36). These studies were conducted under a pancreatic clamp procedure, and nutrients were infused directly into the duodenum to isolate intestinal-specific effects, from other well-known pleiotropic effects of GLP-1 action such as changes in pancreatic hormones and gastric emptying. Current evidence therefore suggests that therapeutic regulation of GLP-1 action may provide benefits in reducing the secretion of atherogenic lipoproteins and CVD risk. Interestingly, in a recent large study, impairment of GLP-1 secretion was an event that may have occurred early in the progression of type 2 diabetes (37). Therefore, preventive strategies that increase GLP-1 secretion and action in overweight and obese, prediabetic individuals warrant further investigation.

GLP-2 stimulates the release of stored chylomicrons. In contrast to the inhibitory effects of GLP-1 on chylomicron secretion, GLP-2 enhances the release of preformed chylomicrons from the intestine. In healthy individuals who are administered intraduodenal lipid infusions, GLP-2 increased apoB48 and TG-rich lipoprotein-TG concentrations within a half an hour of subcutaneous injection (38). GLP-2 injection also stimulated a rapid and transient release of prelabeled chylomicrons from a previous meal and in the absence of an additional meal. The increase was likely a result of the release of stored, presynthesized chylomicrons from the intestine into the circulation. However, it remains unknown whether endogenously secreted GLP-2 stimulates chylomicron secretion and whether this contributes to postprandial lipemia under a range of physiologic conditions.

Another question that remains to be answered is the net effect of gut peptides on intestinal lipoprotein secretion in the progression of type 2 diabetes. Under normal physiologic conditions, the half-life of GLP-2 is longer than GLP-1, which results in more sustained circulating concentrations of the former. Experimental studies in the hamster (39) and in healthy humans (36) suggest that prolonged coinfusion of GLP-1 and GLP-2 or pharmacologic inhibition of DPP-4 activity leads to sustained GLP-1 action and thus net reduction in postprandial lipemia. Yet, mechanisms by which GLP-1 and GLP-2 regulate chylomicron secretion remain unclear. Direct action of GLP-1 to reduce apoB48 secretion was shown in isolated enterocytes (40), but recent experimental evidence also suggests central nervous system regulation of chylomicron secretion by GLP-1 receptors as an alternative mechanism (41). Injection of GLP-2 in pigs and in humans increases intestinal blood flow which provides a potential explanation for how GLP-2 stimulates chylomicron secretion (42, 43). Understanding the factors that control fat absorption will provide novel therapeutic strategies to reduce postprandial excursions of atherogenic lipoproteins. Indeed, enterocyte regulation of dietary lipid entry was the focus of recent scientific efforts in drug development to treat hyperlipidemia and obesity (44, 45). Thus,

future research in this area should address the following questions:

- Do intestinal TG stores serve a regulatory function to control subsequent energy balance?
- Do subjects with ectopic lipid stores in liver and muscle also have excess lipid stored in the intestine?
- Does body fat or insulin resistance affect dietary FA absorption or secretion of intestinal hormones and do these events affect chylomicron production?
- Does insulin resistance influence which signals control the release of stored intestinal lipid and is the vagus nerve involved?

Another mechanism by which postmeal macronutrient metabolites can affect CVD risk is via influences on the vasculature. The consumption of high-fat meals reduces brachial artery flow-mediated dilation (FMD) at the peak of postprandial lipemia, even in healthy subjects (46). Similarly, postprandial hyperglycemia was shown to transiently impair vascular function in normoglycemic and hyperglycemic adults (6). It is unclear whether reductions in postprandial FMD represent a normal (e.g., physiologic) response that may confer benefit somehow for nutrient disposal. However, studies that investigated prolonged exposure of high concentrations of nutrients to the vasculature support a net negative effect of nutrient toxicity. Through both fat- and glucose-related mechanisms, postprandial oxidative stress appears to play a central role in promoting vascular dysfunction. As described in the next section, postprandial hyperglycemia decreases NO bioavailability, which was the focus of recent advances in the field of postprandial metabolism.

Postprandial Hyperglycemia and Vascular Endothelial Dysfunction

The mechanism by which postprandial hyperglycemia impairs vascular function is incompletely understood, but as reviewed (6) one major contributor is decreased NO bioavailability caused by oxidative stress (47–49). With the use of brachial artery FMD, postprandial hyperglycemia impairs vascular function, consistent with a mechanism of decreasing NO status in an oxidative stress-dependent manner (50). In a crossover design, healthy young men ingested 75 g of glucose or fructose before assessing vascular function at 30-min intervals for 3 h postprandially. Ingestion of glucose, but not fructose, transiently increased plasma glucose with a concomitant decrease in FMD responses. FMD responses were also inversely correlated with postprandial glycemia ($r = -0.82$, $P < 0.05$), supporting the concept that reductions in postmeal hyperglycemia would protect against vascular dysfunction. Malondialdehyde, a biomarker of lipid peroxidation that was measured by HPLC coupled to a fluorescence detector, also increased to a greater extent after glucose ingestion. Malondialdehyde was positively correlated to glycemic responses ($r = 0.87$, $P < 0.05$), whereas it was inversely correlated to FMD ($r = -0.80$, $P < 0.05$), supporting that the impairment in postprandial vascular function is an oxidative stress-dependent event. Oxidative stress is also likely to impair vascular function by increasing asymmetric dimethylarginine (ADMA) relative to Arg (50) (**Figure 3**). ADMA is an endogenously produced competitive inhibitor of endothelial NO synthase (eNOS) that outcompetes Arg for eNOS-mediated synthesis of NO (6). Although circulating ADMA is constitutively low at ~0.5 μM, elevations of 0.1 μM raise CVD risk up to 5.3-fold (51), likely by lowering NO status (52). Consistent with this paradigm, hyperglycemia-induced vascular dysfunction after an oral glucose challenge was associated with increased plasma ADMA/Arg (50). Specifically, glucose ingestion decreased plasma Arg to a greater extent than fructose, whereas postprandial ADMA concentrations were unaffected. However, ingestion of glucose caused greater time-dependent increases in ADMA/Arg relative to that occurring in response to fructose ingestion. Thus, postprandial hyperglycemia is likely to reduce NO bioavailability by limiting Arg availability and increasing ADMA relative to Arg, which is expected to limit substrate availability for NO biosynthesis

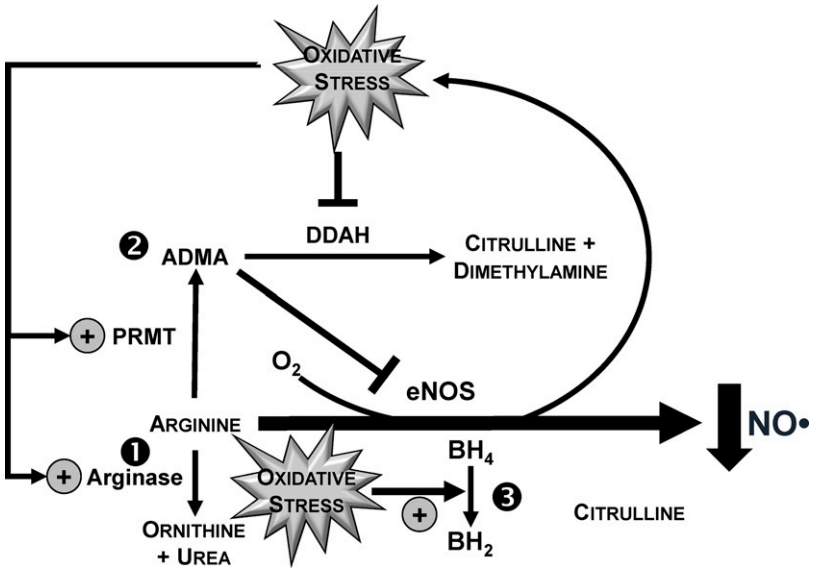

FIGURE 3 Postprandial hyperglycemia induces oxidative stress responses that limit NO bioavailability. Studies in preclinical and clinical models support findings that oxidative stress downstream of acute hyperglycemia reduces NO bioavailability to the vascular endothelium by *1*) increasing the catabolism of arginine in an arginase-dependent manner, *2*) increasing the accumulation of ADMA by upregulating PRMT activity and downregulating DDAH activity, and *3*) increasing the oxidation of BH_4 to BH_2. The net effect of greater ADMA relative to arginine is an increase in the competitive inhibition of eNOS binding toward arginine. ADMA, asymmetric dimethylarginine; BH_2, dihydrobiopterin; BH_4, tetrahydrobiopterin; DDAH, dimethylarginine dimethylaminohydrolase; eNOS, endothelial NO synthase; PRMT, protein arginine methyltransferase.

while competitively inhibiting eNOS. Although not yet investigated clinically, oxidative stress also decreases NO bioavailability by oxidizing tetrahydrobiopterin to dihydrobiopterin, which limits tetrahydrobiopterin binding to eNOS to prevent NO synthesis (53) (Figure 3). Studies in endothelial cells show that 48 h of high-glucose treatment decreases the ratio tetrahydrobiopterin:dihydrobiopterin (54). In healthy adults, intra-arterial infusion of 6R-tetrahydrobiopterin prevented decreases in endothelium-dependent vasodilation that were otherwise induced by an oral glucose challenge (55), supporting that postprandial hyperglycemia impairs vascular function by reducing tetrahydrobiopterin availability. However, the extent to which postprandial hyperglycemia directly diminishes vascular function by lowering NO bioavailability in a tetrahydrobiopterin-dependent manner requires investigation.

Dietary approaches to regulate postprandial vascular function. Although postmeal hyperglycemia transiently impairs vascular function (6), few studies have investigated dietary approaches that may provide vasoprotective activities during the postprandial period. Such strategies could target vascular dysfunction directly by attenuating postprandial hyperglycemia or indirectly by mitigating pathogenic responses downstream of hyperglycemia that promote vascular dysfunction. Although ingestion of various carbohydrate types was examined for their effects on the postprandial glycemia index (56), few studies have linked their differential glycemic responses to postprandial vascular function. Actively under way are studies that examine starch ingestion (50 g) on vascular health to support that postprandial increases in blood glucose are attenuated (57) relative to the ingestion of glucose (75 g) (50). However, despite a lowering in the magnitude of hyperglycemia, postprandial brachial artery FMD after the ingestion of starch was lowered at the same time point that corresponded to peak blood glucose (60 min), suggesting that vascular function continues to be impaired despite reducing hyperglycemia. Continued studies are needed to examine whether attenuations in postprandial hyperglycemia also mitigate oxidative stress responses that would be expected to reduce NO bioavailability.

The involvement of oxidative stress in response to a glucose challenge supports dietary antioxidants in potentially mitigating impairments in vascular function independent of changes in hyperglycemia. Title et al. (58) demonstrated that co-administration of vitamin C (2 g) and α-tocopherol (800 IU) with an oral glucose challenge (75 g) maintained brachial artery FMD responses that were otherwise impaired by ingesting glucose alone. However, it remains unclear how these vasoprotective activities occurred. Neither plasma antioxidant was measured during the 4-h postprandial period, and the time to maximal plasma concentration of α-tocopherol occurs at ~12 h after oral ingestion (59, 60). In contrast, vitamin C is water soluble and achieves peak plasma concentrations at ~150 min after oral ingestion (61), supporting that the acute vasoprotective activities observed after co-antioxidant ingestion were largely mediated through vitamin C rather than their combined actions. To better evaluate vasoprotective effects of vitamin E, a crossover study was conducted in normoglycemic adults in which they completed an oral glucose challenge (75 g) without or with 5 d of prior supplementation of a γ-tocopherol-rich supplement (500 mg γ-tocopherol/d) (62). In response to short-term supplementation, plasma γ-tocopherol concentrations increased from 2.2 μM up to 6.6 μM, and γ-carboxyethyl-hydroxychromanol (γ-CEHC), the physiologic metabolite of γ-tocopherol, increased from 0.32 μM up to 3.1 μM; plasma α-tocopherol was unaffected. Although improvements in γ-tocopherol status did not affect postprandial hyperglycemic responses after an oral glucose challenge, supplementation protected against postprandial decreases in FMD responses that otherwise occurred after glucose ingestion (62). Maintenance of vascular function by vitamin E supplementation was also accompanied by a blunting in postprandial malondialdehyde concentrations and ration of ADMA to Arg. These findings suggest that γ-tocopherol and/or γ-CEHC protected against hyperglycemia-induced vascular impairments, likely in an oxidative stress-dependent manner that improves NO bioavailability but independent of any changes in glycemic responses. Additional research is needed to identify the independent and additive contributions of γ-tocopherol and γ-CEHC in regulating vascular dysfunction and the extent to which other dietary antioxidants similarly protect against postprandial hyperglycemia-mediated impairments in vascular health.

Inflammation during postprandial hyperglycemia-mediated vascular dysfunction. Clear evidence implicates oxidative stress in contributing to hyperglycemia-mediated vascular dysfunction (6). Although studies in vitro consistently show that high-glucose treatments (typically ~25 mM for 24 h) induce NFκB-dependent inflammatory responses, findings from clinical studies were equivocal with some showing induction of postprandial inflammation in response to acute hyperglycemia, whereas others show no changes in proinflammatory mediators (6). Studies in adults without diabetes support this relation with 2-h blood glucose concentrations after an oral GTT to predict the magnitude of circulating C-reactive protein (63). In healthy adults, plasma TNFα concentrations and NFκB binding activity increase at 1 h after an oral glucose challenge (64). In contrast, studies specifically aimed at defining postprandial vascular function show that a number of inflammatory proteins and adhesion molecules (i.e., C-reactive protein, TNFα, IL-6, IL-10, myeloperoxidase, intercellular adhesion molecule 1, vascular cell adhesion molecule 1, E-selectin) are unaffected in response to a 75-g glucose challenge (50) or supplementation of a γ-tocopherol-rich supplement before administration of a 75-g glucose challenge (62) in young, normoglycemic adults. Additional study is needed to address the role of inflammation on glycemia-mediated vascular dysfunction and whether these inconsistent study outcomes are due to differences in participant age or the presence of underlying morbidities that may exacerbate postprandial inflammation. Future research in this area should also focus on the following questions:

- Are there additional NO-independent mechanisms during post-meal hyperglycemia-mediated vascular dysfunction?
- How do mixed-meals affect hyperglycemia-induced impairments in postprandial vascular function?
- What is the metabolic origin of reactive oxygen species that contribute to oxidative stress (e.g., mitochondrial, activated inflammatory cells)?

Although findings of meta-analyses support the use of brachial artery FMD in predicting future CVD events (65, 66), more research is needed to establish clear associations between postprandial FMD responses and the risk of CVD and the basic mechanisms to support these relations. Further, one of the most important research areas that has emerged over the past decade is the impact of circadian disruption on metabolism. In this regard, sleep restriction was also found to impair FMD responses, consistent with the growing epidemiologic evidence that associates short sleep duration with increased cardiovascular events (67). The final section of this review describes recent studies to investigate metabolic mechanisms by which lack of sleep increases type 2 diabetes and cardiometabolic risk.

Insufficient Sleep and Dysregulation of Nutrient Metabolism

Normal sleep is regulated by sleep-wake homeostasis and circadian rhythmicity, which are both known to affect peripheral energy metabolism via neuronal and hormonal pathways (68). Despite current recommendations that adults should sleep ≥7 h/night to promote optimal health (69), sleep curtailment has become an increasingly prevalent behavior in modern society. Estimates indicate that average sleep duration has decreased by 1.5–2.0 h in the past half century. According to the National Sleep Foundation (70), as many as one-third of Americans reported not getting enough sleep by comparing the hours of sleep they said they needed with the hours of sleep they were actually getting on workdays or weekdays. Overall, >50% of the respondents agreed that not getting enough sleep affected their job performance, relationships with family or friends, and ability to perform everyday activities.

Sleep restriction and insulin resistance. In multiple epidemiologic studies, short sleep duration is associated with increased risk of obesity, type 2 diabetes, hypertension, and CVD, and these observational data were discussed comprehensively in 2 recent reviews in *Advances in Nutrition* (71, 72). Emerging data in this field have suggested that an increased consumption of energy dense and highly palatable foods in the sleep-deprived state is explained by alterations in hunger hormones, hedonic pathways, and the time of intake (71). Notably, the present discussion of this topic focuses on the nocturnal and subsequent nutrient handling throughout the day that occurs in humans after sleep restriction under experimental conditions. In well-controlled laboratory settings, insufficient sleep that results from either short sleep duration and/or circadian disruption is associated with marked reductions in insulin sensitivity and glucose intolerance (9, 73–79). Moreover, reduced sleep quality in healthy volunteers, induced experimentally by acoustic stimuli, resulted in decreased insulin sensitivity and glucose tolerance as assessed by an intravenous GTT (80). Potential mechanisms that play a role in the link between insufficient sleep and insulin resistance include alterations in brain glucose utilization, increased sympathetic activity, hyperactivity of the hypothalamic-pituitary axis, altered adipokine secretion, and elevated plasma FFAs. Acute elevations in circulating FFA concentrations are associated with insulin resistance (81–84). Under normal conditions, a marked diurnal variation in circulating FFA concentrations is observed in healthy subjects with peak concentrations occurring in the middle of the night while declining toward the morning (85).

To address the role of FFAs in producing insulin resistance associated with sleep restriction, healthy young men were studied under controlled laboratory conditions with 4 consecutive nights of 8.5 h in bed (normal sleep) or 4.5 h in bed (sleep restriction) in a randomized order. Twenty-four-hour blood profiles of FFAs and hormones, including growth hormone, noradrenaline, and cortisol, were assessed simultaneously (86). Insulin sensitivity was measured with the use of a frequently sampled intravenous GTT. When sleep was restricted, FFA concentrations remained elevated throughout the night and early morning hours during the prolonged fasting state (86). However, subsequent daytime FFA concentrations were similar between sleep conditions, suggesting that sleep restriction may differentially affect FFA concentrations during fasting versus fed states. Sleep restriction was also associated with extended nocturnal growth hormone secretion at night, increased norepinephrine concentrations during the early nighttime and early morning hours, and increased evening cortisol concentrations. The elevation in FFAs was correlated with prolonged nocturnal growth hormone secretion ($r = 0.81$, $P < 0.0001$) and higher early morning noradrenaline concentrations ($r = 0.55$, $P = 0.015$). Insulin sensitivity was impaired by 23% after sleep restriction, and the reduction in insulin sensitivity correlated with the increase in nocturnal FFA concentrations ($r = -0.52$, $P = 0.05$). Elevations in norepinephrine concentrations support the hypothesis that augmented sympathetic drive may be a potential mediator of the metabolic consequences associated with sleep loss. In summary, this randomized, controlled laboratory study found that elevated FFAs contribute, at least in part, to insulin resistance and may lead to the elevated diabetes risk associated with long-term sleep restriction (86).

These more comprehensive findings extend earlier studies of sleep restriction when FFA concentrations were measured only in the morning hours over a limited number of time points (87, 88). These findings also suggest a mechanism of adipoctye cell resistance to the antilipolytic effects of insulin which is consistent with impaired intracellular insulin signaling in adipose tissue that occurs after sleep restriction (76, 89). Future mechanistic studies (e.g., utilization of pharmacologic agents to suppress FFAs) will be necessary to support a causal role for FFAs in insulin resistance induced by sleep loss.

Circadian disruption has also been associated with adverse metabolic effects (79, 90), and evidence exists to support the importance of clock genes (*CLOCK* and *BMAL1*) in regulating lipolytic activity in adipose tissue (91).

Effects of sleep restriction on postprandial metabolism. As discussed in the section above, most studies to date have focused on investigating the impact of insufficient sleep on metabolic events that occur early in the morning hours and during the fasted state. However, whether reduced insulin sensitivity in the sleep-deprived state may also feed forward to impair postprandial responses throughout the next day is not well understood. In the protocol of Broussard et al. (86) discussed above, healthy men underwent 4 nights of sleep restriction after which a 12-h period of metabolism was monitored, in the postprandial state. Sequential, identical, carbohydrate-rich meals were fed at breakfast (0900), lunch (1400), and dinner (1900). Postmeal glucose responses tended to be increased ($P = 0.061$), and insulin concentrations were significantly increased ($P = 0.045$) after breakfast only, suggesting that prolonged sleep restriction impaired glucose metabolism at breakfast, but that the sleep effect did not persist after the later meals. By contrast, another study in healthy men showed that metabolic impairments may accumulate throughout the day (92). In this study, Reynolds et al. (92) fed 3 identical meals (53% of energy from carbohydrate, 27% from fat, and 17% from protein) on the fifth night of sleep restriction (4 h in bed) and monitored 24-h interstitial glucose concentrations by a continuous glucose monitoring system. Relative to normal sleep (10 h in bed), sleep-restricted glucose concentrations were consistently elevated after each of the 3 meals, particularly after dinner during the nighttime hours. In other sleep restriction studies, subjects consumed additional energy after dinner, when awake (93, 94); thus, the sleep-restricted impairment in postprandial glucose metabolism may worsen health even more, if it also leads to increased energy intake of foods with high glycemic index at night after dinner. Interestingly, in a study that examined sex differences during sleep restriction, men exhibited a greater increase in energy intake during the late-night hours relative to women (94).

The effect of sleep restriction on postprandial lipid responses is also understudied. Wehrens et al. (88) investigated the effect of total sleep deprivation on lipid metabolism and found that postmeal TG responses were higher after a night of sleep recovery than after total sleep deprivation. These data suggest that metabolic abnormalities may appear after a stressor was removed and that inconsistent sleep patterns (switching between working nights and days) may be more detrimental than constant night-shift work. Another important area completely lacking in information, to our knowledge, is the impact of sleep restriction on amino acid metabolism. Given that sleep deprivation is associated with increased insulin resistance, more research is needed to identify whether it impairs whole-body protein synthesis and degradation. Future studies could be designed to address this issue and other questions, as follows:

- What are the independent effects of dysregulated circadian timing on FFA metabolism?
- Do men and woman respond differently to sleep restriction?
- What are the effects of sleep restriction on sarcopenia in aging and disease processes?
- Can correcting sleep restriction with adequate sleep improve cardiometabolic outcomes?

Conclusions and Future Directions

Dysfunctional metabolism of macronutrients characterizes the pathophysiology of obesity and insulin resistance, and the altered events downstream of metabolic flux clearly contribute to accelerated CVD progression. The influence of acute stressors on circadian energy metabolism has gained increased attention because these factors may be responsible for accumulated long-term disease risk (**Figure 4**). Understanding the regulation of enterocyte lipid handling

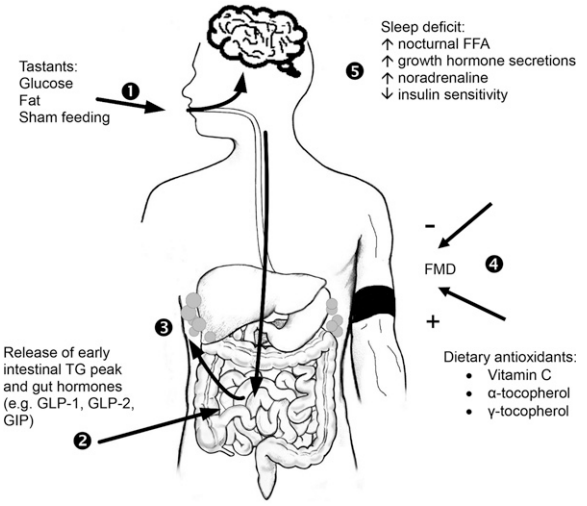

FIGURE 4 The interplay between macronutrient metabolism and cardiometabolic risk may encompass the initial encounter of dietary fat and carbohydrate with taste buds through their eventual site of storage in the body and can be influenced by basal conditions present early in the day. *1*) At the onset of a meal, putative taste receptors signal through the taste buds to the brain, and *2*) the signal is hypothesized to be transported to the vagus nerve to cause the release of an early intestinal TG peak and gut hormones (e.g., GLP-1, GLP-2, GIP). *3*) This taste/intestinal lipid axis may provide a potential feed-forward signal (arrow to adipose) of impeding dietary load by controlling lipid secretion and storage in adipose. *4*) On feeding, postprandial excursions of lipids or glucose can impair FMD which is indicative of endothelial dysfunction, whereas dietary components that attenuate oxidative stress, for instance, exhibit vasoprotective activities during acute hyperglycemia. *5*) Sleep deficit results in nocturnal FFAs that remain elevated throughout the next morning, along with prolonged nocturnal growth hormone secretion and higher early morning noradrenaline concentrations. These metabolic adaptations in the sleep-deprived state may accumulate to impair postmeal responses during the day. FMD, flow mediated dilation; GLP, glucagon-like peptide; GIP, gastric inhibitory peptide. Adapted from reference 95 with permission.

throughout the day will provide novel therapeutic strategies to reduce CVD risk. Furthermore, clinical studies have provided clear evidence that prolonged postprandial hyperglycemia transiently impairs vascular function. In this regard, targeting postmeal hyperglycemia will be particularly important, given recent data to indicate that dietary energy intakes of Americans have increased by nearly 200 kcal/d, which was attributed partly to greater intakes of refined grains, sugars, and starches (96). Experimental laboratory studies have shown that insufficient sleep, which is increasingly common in modern society, is associated with adverse effects on energy metabolism that lead to poor nutrient handling early during the day and later during the nighttime hours. Further, it is important to appreciate that the variability among subjects in postprandial responses may be due to differences in enteral lipid handling, postabsorptive events in the vasculature, or lifestyle factors such as restricted sleep. As the field of postprandial metabolism advances, it is likely that future discoveries that underscore the interplay between acute stressors and macronutrient metabolism will become increasingly important. To support advancements in the clinical management of disease, future studies should focus on individual responses to meal components and on optimizing sleep and circadian factors to reduce cardiometabolic risk.

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