Journal of the American College of Cardiology Vol. 51, No. 3, 2008

Published by Elsevier Inc.
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2007.10.016

STATE-OF-THE-ART PAPER

Dietary Strategies for Improving Post-Prandial Glucose, Lipids, Inflammation, and Cardiovascular Health

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The highly processed, calorie-dense, nutrient-depleted diet favored in the current American culture frequently leads to exaggerated supraphysiological post-prandial spikes in blood glucose and lipids. This state, called post-prandial dysmetabolism, induces immediate oxidant stress, which increases in direct proportion to the increases in glucose and triglycerides after a meal. The transient increase in free radicals acutely triggers atherogenic changes including inflammation, endothelial dysfunction, hypercoagulability, and sympathetic hyperactivity. Post-prandial dysmetabolism is an independent predictor of future cardiovascular events even in nondiabetic individuals. Improvements in diet exert profound and immediate favorable changes in the post-prandial dysmetabolism. Specifically, a diet high in minimally processed, high-fiber, plant-based foods such as vegetables and fruits, whole grains, legumes, and nuts will markedly blunt the post-meal increase in glucose, triglycerides, and inflammation. Additionally, lean protein, vinegar, fish oil, tea, cinnamon, calorie restriction, weight loss, exercise, and low-dose to moderate-dose alcohol each positively impact post-prandial dysmetabolism. Experimental and epidemiological studies indicate that eating patterns, such as the traditional Mediterranean or Okinawan diets, that incorporate these types of foods and beverages reduce inflammation and cardiovascular risk. This anti-inflammatory diet should be considered for the primary and secondary prevention of coronary artery disease and diabetes. (J Am Coll Cardiol 2008;51:249–55) © 2008 by the American College of Cardiology Foundation

Systemic inflammation is increasingly recognized as an important mediator of coronary artery disease (CAD) and other common chronic degenerative diseases such as diabetes and Alzheimer dementia (1). In many individuals a maladaptive diet is a major underlying cause of this chronic inflammation (1,2). High-calorie meals rich in processed, easily digestible, quickly absorbable foods and drinks can lead to exaggerated post-prandial elevations in blood glucose and triglycerides (3). Accumulating data from multiple lines of evidence suggests that this condition, termed post-prandial dysmetabolism, is an important and largely unrecognized fundamental disturbance involved in the genesis of inflammation and atherosclerosis (3).

Exaggerated post-prandial spikes in glucose and lipids generate excess free radicals (or reactive oxygen species) that can trigger a biochemical cascade resulting in inflammation, endothelial dysfunction, and sympathetic hyperactivity (4,5). These post-prandial changes when repeated multiple times daily eventually lead to atherosclerotic risk factors and CAD. Dietary and lifestyle factors play a central role in the etiology of post-prandial dysmetabolism (3). The hypothesis of this review is that specific dietary strategies can dramatically and immediately improve post-prandial glucose and lipid levels, inflammation, and endothelial function, and if used in the long-term will also improve cardiovascular (CV) health.

Post-Prandial Hyperglycemia

Recent studies indicate that about one-third of American adults and two-thirds of CAD patients have abnormal glucose homeostasis (6,7). A significant proportion of these at-risk individuals will have a fasting glucose level in the nondiabetic range (<126 mg/dl) but would show hyperglycemia diagnostic of impaired glucose tolerance (>140 mg/dl) or diabetes (>200 mg/dl) after an oral glucose tolerance test or a meal.

Continuous linear direct relationships exist between glucose levels after a glucose challenge and the risks of both CV death and all-cause mortality (8). At only 80 mg/dl the CV risk of post-prandial or post-challenge glycemia begins to increase; by 140 mg/dl, the point at which we traditionally only begin to classify patients as glucose intolerant or pre-diabetic, the risk is already increased by 58% (9,10) (Fig. 1).

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Manuscript received August 16, 2007; revised manuscript received October 5, 2007, accepted October 7, 2007.

JACC Vol. 51, No. 3, 2008
January 22, 2008:249–55

Abbreviations and Acronyms

CAD = coronary artery disease

CV = cardiovascular

Post-Prandial Hyperlipemia

Recent studies of healthy individuals indicate that a single meal high in saturated fat will cause immediate increases in triglycerides, oxidative stress, and inflammation, which causes corresponding post-meal worsening of endothelial dysfunction, vasoconstriction, and systolic blood pressure (11,12). Post-prandial hyperlipemia, manifest as elevated levels of triglycerides, chylomicrons, and remnant lipoproteins, causes oxidative stress and inflammation, and independently potentiates the adverse effects of post-prandial hyperglycemia (13). These elevated and protracted post-meal lipid levels are common manifestations of insulin resistance and the metabolic syndrome (14).

Triglycerides are traditionally measured in the fasting state—typically the lowest triglyceride level of the day. Two large recently published cohort studies involving over 40,000 individuals found that post-prandial hypertriglyceridemia was associated with increased risk of CV events, whereas fasting triglyceride level was not (15,16). Post-prandial triglyceride levels are also directly related to angiographic progression of coronary and carotid atherosclerosis (3). Subanalyses of 3 randomized trials showed that lowering levels of elevated triglycerides by 20% to 40% reduced CAD rates by approximately 30% to 40% (15).

How the Modern Diet Causes Inflammation

Excessive ingestion of calorie-dense, easily digestible foods causes abnormal surges in blood glucose and triglyceride levels (11–13). This bolus of energetic substrate overwhelms the metabolic capabilities of the mitochondria in the overnourished muscle and adipose tissues. Glucose and free fatty acids flood the Krebs cycle, stimulating an excess of the reduced form of nicotinamide adenine dinucleotide production, which outstrips the capacity of oxidative phosphorylation and drives the transfer of single electrons to oxygen, creating free radicals such as superoxide anion (17). Post-prandial glucose excursion correlates directly with the ensuing increase in free radicals (Fig. 2). This post-prandial oxidant stress acutely triggers atherogenic changes, including increases in low-density lipoprotein oxidation, sympathetic tone, vasoconstriction, and thrombogenicity (5,17). Meal-induced inflammation is evidenced by immediate increases in C-reactive protein, cytokines, and endothelin-1 (Fig. 3) (3,17). Even hyperglycemic spikes induced artificially using intravenous glucose infusions in lean nondiabetic individuals have been shown to markedly increase free radical generation (18).

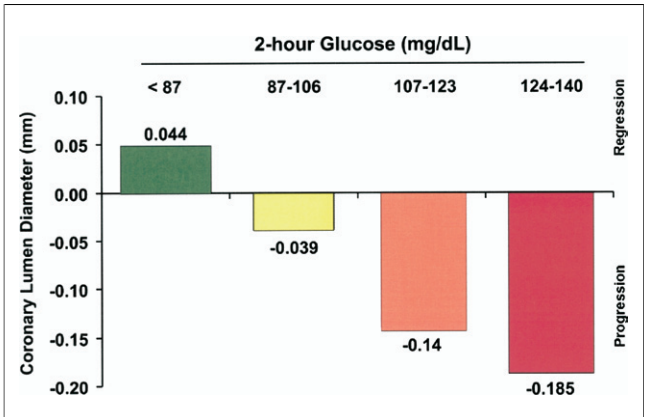

Figure 1 Post-Challenge Glucose and Coronary Atherosclerosis Progression

Patients with normal glucose tolerance who had a post-prandial glucose level of <87 mg/dl had coronary regression. The remaining patients had coronary progression in proportion to the increase in post-prandial glucose. Data from Mellen et al. (10).

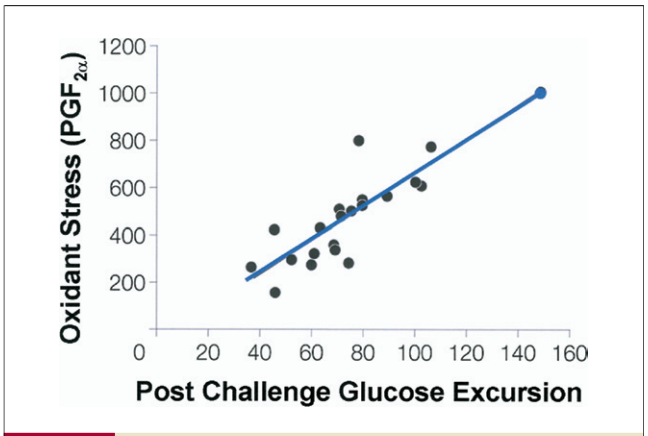

Figure 2 Glucose Excursion Directly Related to Oxidant Stress

Linear correlation between post-prandial glucose excursions and urinary excretion of 8-iso prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), a measure of oxidant stress. Reprinted with permission (17).

Therapies for Post-Prandial Dysmetabolism

Promising pharmacologic approaches to the normalization of post-prandial dysmetabolism are evolving. However, resorting to drug therapy for an epidemic caused by a maladaptive diet is less rational than simply realigning our eating habits with our physiological needs (2). The traditional Mediterranean and the Okinawan diets, which are rich in minimally processed natural foods that are low in caloric density but high in nutrient density, have been associated with improved CV health and longevity (1,19). These diets are closer to the ancestral hunter-gatherer eating patterns for which modern humans remain genetically adapted (20). Specifically, diets that include large amounts of fresh unprocessed plants, with moderate levels of lean protein and beneficial fats (such as omega-3 and monounsaturated fats) and low levels of processed carbohydrates and saturated and trans fats, and that are rich in antioxidants substantially improve post-prandial glucose and lipid levels (19).

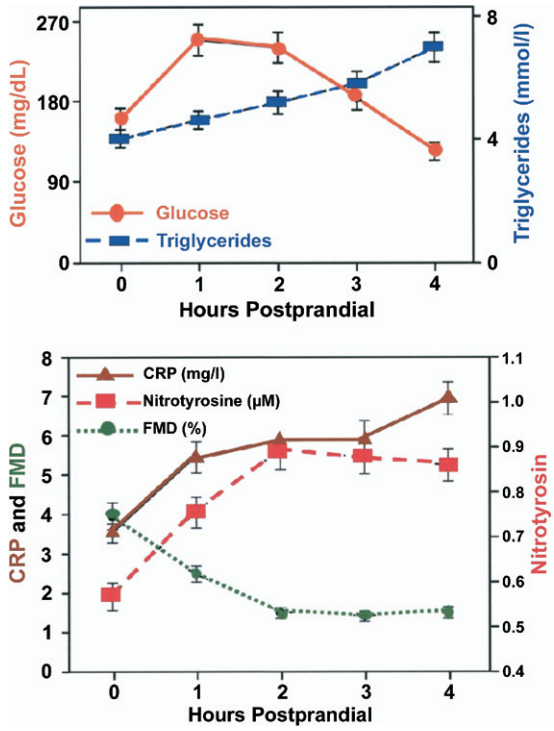

Figure 3 Post-Prandial Stress

The immediate deleterious effects of a beverage containing 75 g glucose mixed with 700 kcal/m^2 of whipping cream. Within 2 to 4 h glucose and triglyceride levels double, causing immediate oxidant stress (nitrotyrosine), inflammation (C-reactive protein [CRP]), resulting in deterioration in endothelial function. FMD % = percent flow-mediated dilation. Data from Ceriello et al. (41).

Type and Amount of Carbohydrate Consumed

The amount and type of carbohydrate consumed with a meal is a major determinant of the post-prandial glucose excursion (21). The glycemic index of a food is defined as the incremental increase in the area under the post-prandial glucose curve after ingestion of 50 g of a specific food compared with that noted after ingestion of 50 g of oral glucose. A meal such as white bread and jelly with a glycemic index of 80 will result in a 2-fold higher incremental increase in glucose compared with an isocaloric meal of whole-grain bread and peanut butter with a glycemic index of 40. Most studies show that diets rich in high-glycemic-index, low-fiber foods independently increase the risk of both CV disease and type 2 diabetes (19,21).

Minimally processed plants such as vegetables, fruits, nuts, seeds, and grains generally increase post-prandial glucose and triglycerides to a lesser degree than do processed foods (22). Ideal carbohydrate foods for improving post-prandial dysmetabolism include green leafy vegetables such as broccoli and spinach, or fruits such as grapefruits and cherries. Their lower caloric density and glycemic indexes and higher fiber and water content induce less glucose excursion after a meal, whereas their antioxidant phytonutrients dampen down the oxidant stress that is inherently generated when glucose or fatty acids are burned in the Krebs cycle (2). Dietary antioxidants such as those present in deeply pigmented plant-based foods and drinks such as berries, red wine, dark chocolate, tea, and pomegranates help to protect the vascular endothelium from post-prandial oxidant stress and inflammation independently of their effects on post-prandial glucose and triglyceride levels (2,23). Cinnamon is a calorie-free herb rich in antioxidants that, when added to a high-glycemic-index meal, significantly reduces the post-prandial glucose excursion, partly by slowing gastric emptying (24).

Excess intake of processed carbohydrates sets up a vicious cycle whereby the transient spikes in blood glucose and insulin early after a meal trigger reactive hypoglycemia and hunger (25). The chronic consumption of a diet high in processed carbohydrates leads to excess visceral fat, which increases both insulin resistance and inflammation and predisposes to diabetes, hypertension, and CV disease (25). In contrast, restriction of refined carbohydrates will improve the post-prandial levels of both glucose and triglycerides and can reduce intra-abdominal fat, particularly in individuals with insulin resistance (25).

The amount of carbohydrate consumed is equally important as the glycemic index. Small quantities of high glycemic index foods such as white rice, glucose, or potatoes will have a proportionally smaller effect on post-prandial glucose spikes than larger quantities of these foods (26). On the other hand, even low glycemic index foods such as legumes (e.g., lentils) when consumed in large quantities can cause substantial post-prandial glucose spikes (26). Thus, portion control is of fundamental importance to the short- and long-term health effects of any diet. The portion size inflation that has transpired in American restaurants in recent decades is not just contributing to the obesity crisis but also is causing immediate toxic effects throughout the vascular system in the person who consumes such a meal (16).

Dietary fiber is effective at delaying gastric emptying, slowing digestion, and reducing post-prandial excursions of both glucose and triglycerides (27). Minimally processed plant-based foods are natural sources of soluble and insoluble fiber that improve post-prandial dysmetabolism, reduce oxidant stress and inflammation, and lower the risks of CAD and diabetes (19,22,27).

Nuts, Olive Oil, and Fish Oil

Nuts, when consumed with a meal, will significantly reduce the post-prandial glucose excursion by slowing digestion. Recent studies show that almonds, pistachios, or peanuts, when eaten along with high glycemic index carbohydrates such as white bread or mashed potatoes, will reduce the post-prandial glucose area under the curve by approximately 30% to 50% (28) (Fig. 4). Importantly, nuts also decrease meal-induced oxidative protein damage because they lower

JACC Vol. 51, No. 3, 2008
January 22, 2008:249–55

post-prandial oxidative stress and additionally provide antioxidants (29).

A recent trial randomized 772 subjects at high risk for CAD to a low-fat diet or a Mediterranean-style diet supplemented with either walnuts (30 g/day) or virgin olive oil (1 l/week). This trial found that after 3 months the Mediterranean diets supplemented with either nuts or olive oil produced clinically significant reductions in systolic blood pressure, fasting glucose, and inflammatory biomarkers compared with the low-fat diet (1).

Epidemiologic studies consistently indicate that consumption of nuts at least 5 times per week will reduce CAD and diabetes risks by 20% to 50% (29). Tree nuts are comprised predominantly of monounsaturated fats and are a rich source of antioxidants, fiber, phytosterols, magnesium, and folic acid, which might beneficially influence CV risk. Replacing refined carbohydrates with monounsaturated fats (using nuts and/or olive oil) will reduce post-prandial hyperglycemia and hypertriglyceridemia, increase high-density lipoprotein, and decrease oxidative stress (1,2). One practical way to accomplish this is to substitute nuts (all of which have very low glycemic indexes) for the sugary and starchy snack foods that are staples in the American diet.

Fish oil (omega-3 fatty acids) lowers post-prandial triglyceride levels by 16% to 40% in a dose-dependent fashion, in part by upregulating lipoprotein lipase activity and accelerating the clearance of chylomicrons (30). Thus, some of the documented anti-inflammatory and cardioprotective activities of omega-3 fatty acids may be conferred in part by significant improvements in post-meal lipid levels (31).

Vinegar

A mixture of vinegar and olive oil is the traditional salad dressing used in the Mediterranean diet. The consumption of vinegar with meals was used as a home remedy for diabetes before the advent of pharmacologic glucose-lowering therapy. Indeed modern studies indicate that vinegar significantly reduces post-meal glycemia, probably because acetic acid slows gastric emptying and thus delays carbohydrate absorption and improves satiety. Recent studies show that 1 to 2 tablespoons of vinegar, when added to a meal containing high-glycemic-index foods such as white bread or white rice, will both: 1) lower post-prandial glucose by 25% to 35% (Fig. 5), and 2) increase post-meal satiety by more than 2-fold (32). Thus the addition of vinegar to a standard meal can not only improve the meal-induced oxidant stress by blunting the post-prandial glucose excursion, but also can increase and prolong satiety, which should help to reduce food cravings and lower caloric intake over the subsequent 2 to 4 h. Finally, vinegar with olive oil is generally consumed with green leafy vegetables, which have superior nutrient-to-calorie ratios and very low glycemic indexes.

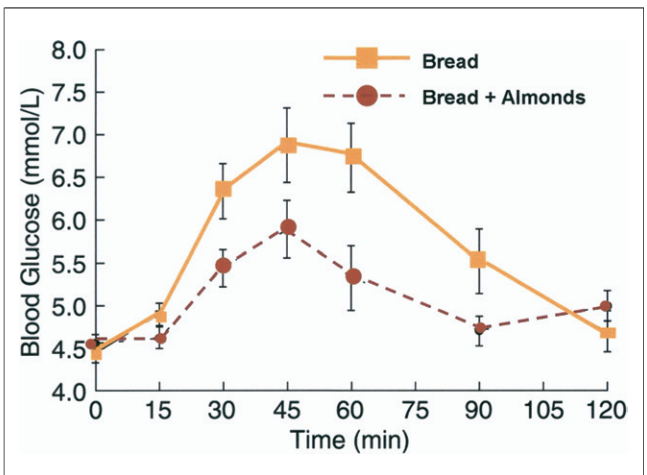

Figure 4 Almonds Reduce Post-Prandial Glucose

The post-prandial increase in the area under the curve for glucose was reduced by 58% when 90 g of almonds were added to a high glycemic index meal ($p = 0.009$). Data from Josse et al. (28).

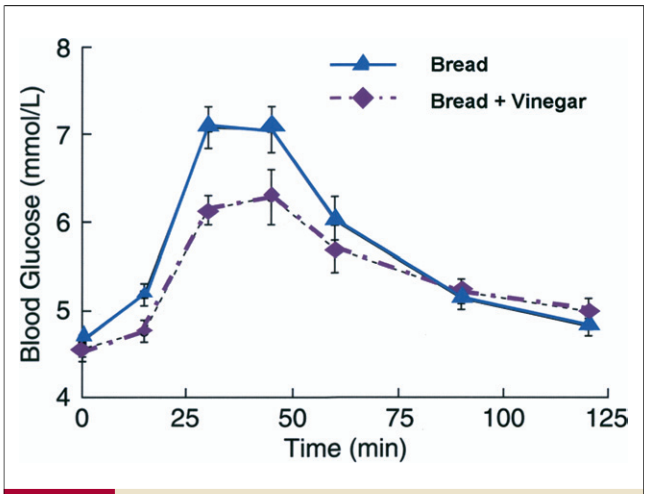

Figure 5 Vinegar Reduces Post-Prandial Glucose

The addition of 2 tablespoons of vinegar to 2 slices of white bread significantly reduced the post-prandial glucose increase. Data from Östman et al. (32).

High-Biological-Quality Protein

Protein is an important component of an anti-inflammatory, cardioprotective diet. Unfortunately, the favored protein sources in the modern diet, such as ground beef, sausage, bacon, and cheese, are high in both calories and saturated fats and tend to worsen post-prandial dysmetabolism (3,11). In contrast, lean protein of high biological value will both reduce post-meal glucose excursion and improve satiety. In a study of healthy individuals, the addition of whey protein to a pure glucose drink lowered the post-prandial blood glucose area under the curve by 56%, and increased the insulin response by 60% (33) (Fig. 6). Additionally, dietary protein has a thermogenic effect whereby it increases the basal metabolic rate, which is not the case with ingested carbohydrates (25). Thus, protein of high biological quality

such as egg whites, fish, game meat (and other very lean red meats), skinless poultry breast meat, and whey protein (or other nonfat dairy protein) when eaten with meals will dampen down post-prandial inflammation and can help prevent obesity (25).

Calorie Restriction and Weight Loss

Weight loss of 5% to 10% or more, particularly when accompanied by decreased abdominal adiposity, lowers post-prandial glucose and reduces the risk of new diabetes (25). Although weight loss can be achieved by any dietary modification that reduces calorie intake, strategies that restrict both processed carbohydrates and unhealthy fats (saturated and trans fats) improve post-prandial dysmetabolism, oxidative stress, and inflammation more effectively than other approaches (1,2,25).

The degree of post-prandial dysmetabolism is closely related to calorie intake. On the extreme end of the spectrum, fasting completely eliminates post-prandial increases in glucose and triglycerides and the ensuing oxidant stress and inflammation. A reduction in calories by approximately 30% below the intake on an ad libitum diet has been shown to improve health and longevity in animal models (34). A similar degree of calorie restriction in humans has been achieved by diets low in processed foods and high in vegetables, fruits, nuts, low-fat dairy, egg whites, soy protein, whole wheat, and lean meat that provides >100% of the daily value for all of the essential nutrients (34,35). This diet was associated with improvements in oxidative stress, inflammation, glucose, insulin sensitivity, blood pressure, lipids, and cardiac function (34,35). Although the ideal caloric intake for optimal health and longevity is yet to be determined in humans, the avoidance of energy-dense processed foods is a logical first step toward the reduction of excess calories.

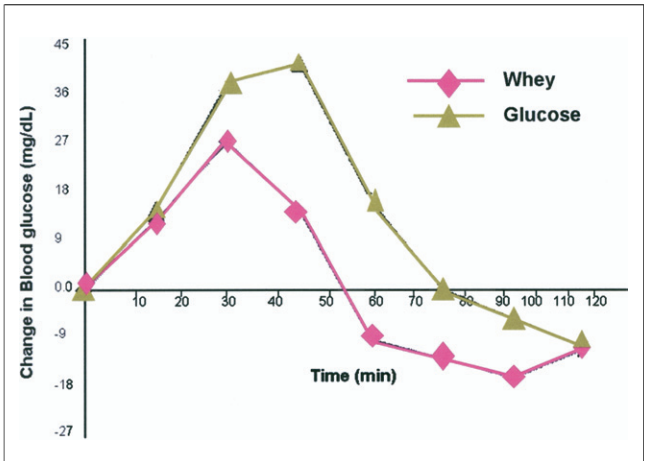

Figure 6 Whey Protein Reduces Post-Prandial Glucose

Increases in blood glucose after either a glucose drink or the same glucose drink mixed with whey protein. Whey protein reduced the area under the curve for blood glucose by 56% ($p < 0.05$). Data from Nilsson et al. (33).

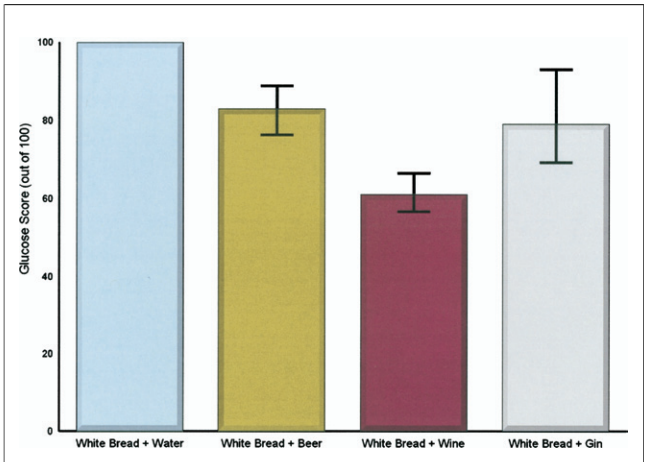

Figure 7 Alcohol Reduces Post-Prandial Glucose

In this group of healthy individuals, 20 g alcohol (approximately 1.5 drinks) in various beverages reduced postmeal glucose by up to 38%. Data from Brand-Miller et al. (37).

Light to Moderate Alcohol Consumption

An extensive body of data shows concordant J-shaped associations between alcohol intake and a variety of adverse health outcomes including CAD, diabetes, stroke, dementia, and all-cause mortality (36). Light to moderate alcohol consumption (0.5 to 1 drink daily for women, and 1 to 2 drinks daily for men) is associated with cardioprotective benefits, whereas increasingly excessive consumption results in proportional worsening of outcomes. Although alcohol increases high-density lipoprotein in a dose-dependent fashion, the effects on glucose homeostasis are nonlinear, conferring benefits at lower doses and harm at higher doses

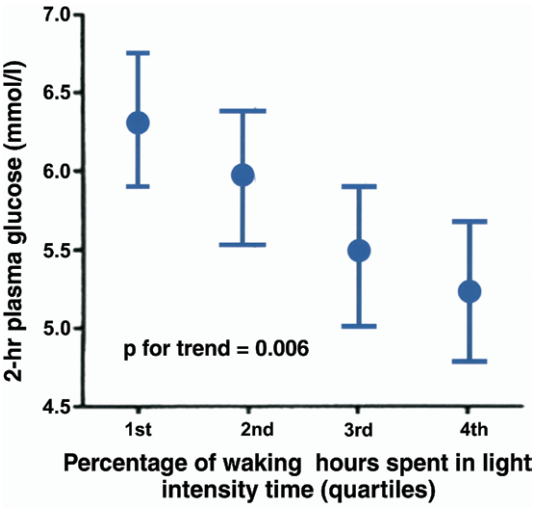

Figure 8 Daily Activity Reduces Post-Prandial Glucose

Cumulative daily light-intensity physical activity was inversely associated with post-prandial glucose levels. Data from Healy et al. (39).

(36). Randomized placebo-controlled trials in healthy nondiabetic individuals showed that 1 to 2 drinks immediately before a meal will significantly lower post-prandial glucose and insulin levels (37) (Fig. 7). Tellingly, the interaction between alcohol intake and post-prandial glucose follows the same J-shaped relationship that is seen between alcohol and systemic inflammation, as well as alcohol and adverse CV events (36).

Consuming a light to moderate amount of alcohol, like exercise, will increase insulin sensitivity and glucose metabolism for the ensuing 12 to 24 h (36). Indeed, daily low-dose alcohol is associated with better health than less frequent consumption (36). Regular light to moderate alcohol intake with the evening meal is traditional in many of the cultures with exceptional health and longevity.

Exercise

Sedentary behavior worsens insulin resistance and magnifies the post-prandial excursions of glucose and triglycerides. In contrast, exercise improves insulin sensitivity predominantly in the skeletal muscles, and acutely lowers glucose and triglyceride levels in a dose-dependent fashion. A single bout of 90 min of moderate-intensity exercise (walking briskly) within 2 h before or after a meal has been shown to lower post-prandial triglycerides and glucose levels by about 50% (3,38). A recent study using continuous objective activity monitoring in 173 nondiabetic individuals found that cumulative daily physical activity, even light-intensity activity, was associated in a dose-dependent fashion with lower 2-h post-challenge glucose levels (but not fasting glucose levels) (Fig. 8). The same study showed that cumulative sedentary time was associated with higher 2-h glucose levels (39).

Physical activity improves inflammation directly by lowering post-prandial glucose, and indirectly by reducing excess abdominal fat (39). Studies show that the body will preferentially mobilize and oxidize fatty acids from adipose tissue during exercise after a low glycemic index meal rather than a high glycemic index meal (40). Thus over time lower glycemic index diets combined with regular exercise may be useful for optimizing loss of excess visceral fat (10,25,40).

Table 1 Steps to Improve Post-Prandial Glucose and Triglycerides

1. Choose high-fiber, low glycemic index carbohydrates such as whole grains, legumes, and vegetables and fruits.
2. Eat lean protein at all 3 meals.
3. Consume nuts on a daily basis, about 1 handful (with a closed fist). Eat with vegetables, berries or other fruits, or grains.
4. Eat a salad of leafy greens dressed with vinegar and virgin olive oil on a daily basis.
5. Avoid highly processed foods and drinks, especially those containing sugar, high-fructose corn syrup, white flour, or trans fats.
6. Keep serving sizes modest.
7. Avoid being overweight or obese; maintain a waist circumference less than one-half of height in inches.
8. Obtain 30 min or more of daily physical activity of at least moderate intensity.
9. Consider consuming 1 alcoholic drink before or with the evening meal (for those without a history of substance abuse).

Summary and Recommendations

The modern calorie-dense, nutrient-poor diet of processed foods, especially when combined with a sedentary lifestyle and abdominal obesity, produces exaggerated post-prandial increases in glucose and lipids, which leads to inflammation and atherosclerosis. In contrast, a diet high in minimally processed, high-fiber, plant-based foods such as low glycemic index vegetables and fruits, whole grains, legumes, and nuts will markedly blunt the post-meal increase in glucose and triglycerides. Additionally, lean protein, fish oil, calorie restriction (ideally induced via avoidance of processed foods and excessive portion sizes), weight loss, vinegar, cinnamon, tea (41), and light to moderate alcohol intake and physical activity positively impact post-prandial dysmetabolism (Table 1).

Acknowledgment
The authors thank Lori J. Wilson for her assistance with preparation of the manuscript and figures.

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