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LIFESTYLE CHANGES: EFFECT OF DIET, EXERCISE, FUNCTIONAL FOOD, AND OBESITY TREATMENT ON LIPIDS AND LIPOPROTEINS

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ABSTRACT

The role of lipids and lipoproteins as risk factors for cardiovascular disease (CVD) is well established. Although CVD remains as the leading cause of mortality in adults, there is a decreasing trend in overall CVD mortality rate over the last two to three decades. This reduction in CVD mortality is largely driven by decreases in coronary heart disease mortality rate. Lifestyle changes remain the cornerstone of management of lipid and lipoprotein disorders and obesity, and are warranted in primary as well as secondary prevention settings. Lifestyle changes recommended for those with high cholesterol levels include adopting a diet low in saturated and *trans* fatty acids, incorporating functional foods rich in bioactive substances such as fiber, antioxidants, plant sterols and stanols, exercising regularly, and maintaining a healthy weight. Based on a large body of evidence, current dietary guidelines uniformly recommend reducing intakes of saturated and *trans* fatty acids with replacement by increasing intake of mono- and polyunsaturated fatty acids. Precision medicine options such as personal preferences regarding food choices and long-term dietary strategies are needed to improve the overall lipid profile. Given the complexity of the individual lifestyle choices, it is not surprising that a substantial heterogeneity regarding outcomes has been observed across studies, underscoring the challenge of accurately assessing effects of lifestyle changes, including diet- or physical activity-based interventions, on the lipid profile and cardiovascular risk. Many factors likely contribute to the variability in observations, including presence of substantial heterogeneity in study settings and designs, publication biases, issues related to self-reported measures of

dietary intakes as well as adherence measurements to study diet. Further, there are a limited number of studies focused on certain types of diet or dietary composition including functional foods or exercise modality. Thus, while existing data offers some insights into fruitful interventions, there is a need to undertake well-designed, controlled, adequately powered, large-scale studies to bring more insights into the role of individual components of lifestyle changes in modifying cardiovascular risk factors and mortality. For complete coverage of all areas of Endocrinology, please visit our on-line FREE web-text, WWW.ENDOTEXT.ORG.

DIET

Historical Perspective

To begin our assessment of the relationship between diet and eating habits, blood lipids, and coronary heart disease (CHD) risk (i.e., the diet-heart hypothesis), we have to travel back to the late 1940s. It all started with Ancel Keys, a researcher at the University of Minnesota, who hypothesized that the epidemic of heart attacks among middle-aged American men was related to their lifestyle and possibly to some modifiable personal characteristics. After exploring his ideas in a group of Minnesota men, providing support on the role of blood cholesterol level, blood pressure, and cigarette smoking—the now-traditional risk factors in predicting heart attacks (1), Keys went on recruiting research collaborators across the world. This was the beginning of “The Seven Countries Study”, the first epidemiological longitudinal study to systematically investigate the relationships between lifestyle, diet, CHD and stroke risks in multiple populations from different regions of the world. Over 12,000 men aged between 40–59 years enrolled as 16 cohorts in four world regions (United States, Northern Europe, Southern Europe, and Japan), where contrasting dietary habits, especially with regard to the proportion of fat calories of different composition, existed (2). Some of the major cardiovascular findings of The Seven Countries Study include the demonstration of a direct and independent association between serum total cholesterol (TC) concentrations and the risk and rates of heart attack and stroke both at the population and at the individual level across diverse cultures (3,4), the importance of the eating pattern defined as the Mediterranean diet in CHD risk (5-8), changes over time in lifestyle and diets of a population in the Mediterranean region and their relation to the rates of heart diseases (9,10), associations between regular exercise, dietary fiber, and body fat (11), and the importance of not being overweight or obese and of regular exercise in maintaining good cardiovascular health (12). Some of the Seven Countries Study findings, establishing the importance of diet, including certain habits and food compositions (saturated fat), in coronary risk and coronary death rates are noted below. The 15-year death rates were related positively to average percentage of dietary energy from saturated fatty acids (SFA), negatively to dietary energy percentage from monounsaturated fatty acids (MUFA), and were unrelated to dietary energy percentage from polyunsaturated fatty acids (PUFA), proteins, carbohydrates, and alcohol in the diet (5). Further, all death rates were negatively related to the ratio of MUFA to SFA. Keys was the first to associate the traditional Mediterranean diet (olive oil as the main fat, high in cereal products, legumes, fruit and vegetables, moderate in fish and low in dairy and meat products, moderate wine consumption) with a low risk of CHD. Together with

his colleagues, Keys played a vital role in the modern definition and promotion of the Mediterranean diet. Walter Willett from the Harvard University further refined the definition of modern Mediterranean diet and its beneficial effects on CHD risk (13-16). Others, in a large prospective cohort study, have confirmed an inverse association between adherence to the Mediterranean diet and the incidence of fatal and non-fatal CHD in initially healthy middle-aged individuals in the Mediterranean region (17). A recent large randomized intervention trail (the PREDIMED Study) among individuals at high cardiovascular risk showed that a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events (18).

Current Dietary Recommendations

Over the years, numerous epidemiological observational and interventional nutritional studies have been conducted, and many meta-analyses and comprehensive reviews have evaluated the overall effects of dietary fats and interventions to reduce saturated fat intake on blood lipid profile as well as risk for CHD. On the basis of these study findings dietary guidelines have universally recommended reducing the intake of saturated fat to lower low-density lipoprotein cholesterol (LDL-C) levels and reduce CHD risk. These recommendations have been central to promote public awareness on healthy eating to improve overall cardiovascular health at a population as well as at an individual level. However, over the years, there have been shift in recommendations with regard to what macronutrients should be used to replace energy lost from lowering of saturated fat. Early Dietary Guidelines for Americans recommended to decrease total and saturated fat intake and to increase accordingly dietary carbohydrates intake, leading to a low or lower fat diet. The current dietary recommendations, however, are to reduce saturated fat intake and increase intakes of dietary MUFA and PUFA, resulting in a moderate fat diet. Other notable shifts include an emphasis on added sugar intake and/or a lessened concern about dietary cholesterol intake.

For adults who would benefit from lowering of LDL-C, the recent 2013 American Heart Association (AHA)/American College of Cardiology Guideline on Lifestyle Management to Reduce Cardiovascular Risk (19) recommends reducing saturated fat intake to 5 to 6% of total calories and reducing the percentage of calories from *trans* fats; and for healthy Americans (>2 years of age), the 2006 AHA Nutrition Committee Scientific Statement advises eating 25 to 35% of daily calories as fats from foods like fish, nuts, and vegetable oils, limiting the amount of saturated fats to 7% of daily calories, limiting the amount of *trans* fats to <1% of total daily calories and cholesterol intake <300 mg/day (20). *Trans* fatty acids are unsaturated fatty acids; however, they are structurally different from the principal unsaturated fatty acids in plant foods and are predominantly formed during food processing (i.e., hydrogenation). Substantial evidence support an association between a high intake of *trans* fatty acids and elevated CHD risk (21), mainly mediated through its deleterious effects on blood lipid profile (22). For more information on *trans* fatty acids and CHD risk, see section “Effects of saturated fat and its replacements on CHD risk”. The National Lipid Association Expert Panel on Familial Hypercholesterolemia (FH) (23) recommends that people with FH restrict intakes of total fat to

25-35% of energy intake, saturated fats should make up <7% of energy intake, and cholesterol intake should be <200 mg/day. The Expert Panel further recommends incorporations of plant stanols or sterol esters and soluble fiber to diets to help to reduce absorption of dietary fat and cholesterol. Consumption of plant stanols and/or sterols at 2 g/day dose reduced LDL-C by ≈10%, and when combined with diets low in saturated fat and cholesterol, the effects were additive (reduced LDL-C even further by ≈20%) (24). The efficacy of plant sterols and stanols as cholesterol lowering agent has been shown to be related to subjects' characteristics, food carrier, frequency, and time of intake (25). Dietary fiber has also been associated with a favorable lipid profile(26) and reduced risk for both cardiovascular disease (CVD) and CHD (27). For more information on plant stanols and sterols and fiber, please see the "Functional Foods" section.

The latest 2015 to 2020 edition of Dietary Guidelines for Americans emphasizes healthy eating patterns and no longer recommends limiting consumption of dietary cholesterol (28) as in previous editions. This shift, however, does not advocate for a lesser importance of dietary cholesterol in building healthy eating patterns and individuals should consume as little dietary cholesterol as possible. Another noteworthy update is on sugar consumption with a specific limit of <10% of daily calories from added sugars. The key recommendation to limiting saturated fat intake <10% of daily calories remains consistent with those in its previous editions. The 2013 American Diabetes Association (ADA) Nutrition Therapy Recommendations for the Management of Adults with Diabetes (29) are in agreement with those for the general population, and the ADA commends the latest edition of Dietary Guidelines for Americans. The 2017 American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease (30,31) note that the intake of saturated fats, *trans* fats and cholesterol should be limited, and consistent with other guidelines, it also recommends to incorporate soluble fiber (10-25 g/day) and plant stanols/sterols (~2 g/day) to diet. The same recommendations with regard to plant sterols/stanols and soluble fiber have been noted in the National Cholesterol Education Program on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel (ATP) III] (32), with specific recommendations for saturated fat intake (<7% of daily calories) and cholesterol (<200 mg/day). Questions, however, remain about specific quantitative recommendations on dietary intakes of MUFA and PUFA, including omega-6 (*n-6*) and omega-3 (*n-3*) fatty acids. The ATP III recommends up to 10% of energy intake as PUFA and up to 20% of energy intake as MUFA, thereby comprising a majority of the recommended 25-35% of total intake (32). The 2014 position paper from the Academy of Nutrition and Dietetics (formerly the American Dietetic Association) set the desirable intakes for *n-6* PUFA at 5-10% energy and for *n-3* PUFA (α linolenic acid) at 0.6-2% energy, with at least 500 mg EPA+DHA/day (33,34). The latter also stated that consumption of MUFA at 15-20% energy, accounting for appropriate PUFA intake, while keeping within 20-35% of energy as fat, is desirable. The 2009 Science Advisory from multiple councils of the AHA summarized evidence on *n-6* PUFA consumption and CHD risk (35). It was concluded that at least 5 to 10% of calories from *n-6* PUFA, particularly linoleic acid, is needed to decrease CHD risk. In contrast, the European Food Safety Authority does not provide specific quantitative recommendations for

dietary fats; instead it recommends the lower the better for saturated fat, as low as possible for *trans* fatty acids, no recommendation for MUFA, with at least 250 mg/day for the *n-3* PUFA (EPA and DHA) and an adequate intake of 4% for the *n-6* PUFA (linoleic acid) (36). Examples of recommendations on dietary fats and cholesterol are given in Table 1.

Table 1. Examples of Recommendations on Dietary Fats and Cholesterol

Guideline/Organization	Target population	Fats	Cholesterol	Others
2014 Academy of Nutrition and Dietetics, position paper	Healthy adults	Total fat: 20-35%; Saturated fat: <7%; *Trans*-fat: <1%; PUFA: *n-6* (3-10% of intake) and *n-3* (0.6-1.2% of intake as α linolenic acid; 500 mg EPA+DHA/day); MUFA: 15-20% of intake		
2013 American Heart Association (AHA)/American College of Cardiology Guideline on Lifestyle Management to Reduce Cardiovascular Risk	People who would benefit from lowering of LDL-C	Saturated fat: 5-6% of daily calories; *Trans*-fat: reduce % of calories		
2013 American Diabetes Association (ADA) Nutrition Guidelines for Adults With Diabetes	Diabetic adults	Total fat: No ideal intake, individualize goals; Saturated fat: <10% of energy intake; *Trans*-fat: limit as much as possible; PUFA: no specific recommendation ; eat fish	<300 mg/day	Fiber: 25 g/day for women; 38 g/day for men (14 g fiber/1,000 kcals/day)

		(particularly fatty fish) ≥2 times/wk; MUFA: Mediterranean-style, MUFA-rich eating pattern		
2017 American Association of Clinical Endocrinologists (AACE)' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis	Adults	Intake of saturated fats and *trans* fats should be limited	should be limited	Soluble fiber: 10-25 g/day; plant stanols/ sterols: ~2 g/day
2011 The National Lipid Association Expert Panel on Familial Hypercholesterolemia (FH)	People with FH	Total fat: 25-35%; Saturated fat: <7% of energy intake	<200 mg/day	Plant sterols and stanols: 2 g/day; soluble fiber:10-20 g/day
2015 Dietary Guidelines for Americans	Adults	Total fat: 20-35%; Saturated fat: <10% of daily calories; *Trans*-fat: as low as possible; PUFA/MUFA: replace saturated and *trans* fats		Carbohydrates : 45-65%; <10% of daily calories from added sugars
2010 The European Food Safety Authority Panel on Dietetic Products	Adults	Total fat: 20-35%; Saturated/*Trans* fats: as low as possible; PUFA: *n-6* (4% of intake as linoleic acid) and *n-3* (0.5% of intake as α linolenic acid; 250 mg EPA+DHA/day)		Carbohydrates : 45-60%; Fiber: 25 g/day

2006 AHA Nutrition Committee Scientific Statement	Healthy Americans (adults & children >2 years old)	Total fat: 25-35%; Saturated fat: <7%; *Trans*-fat: <1% of energy; *n-3* PUFA: consume fish (especially oily fish) at least twice/week	<300 mg/day	
2002 The National Cholesterol Education Program on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults	Adults	Total fat: 25-35%; Saturated fat: <7%; PUFA: up to 10%; MUFA: up to 20% of total calories	<200 mg/day	Plant sterols and stanols: 2 g/day; soluble fiber: 10-25 g/day

Abbreviations: PUFA: polyunsaturated fatty acid; MUFA: monounsaturated fatty acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid;

Heterogeneity in Cholesterol-Raising Effects of Saturated Fatty Acids

Although current dietary guidelines provide no specific recommendations with regard to individual SFA intake, recent research has gathered growing appreciation to the unique properties of individual SFA in altering blood lipid profile. Individual SFA have diverse biological and cholesterol-raising effects. The chain length of SFA plays an important role in defining biological functions, such as susceptibility to oxidation and solubility in water, as well as effects on blood lipids and lipoproteins. The most commonly consumed SFA are palmitic acid (16:0; major source: vegetable oil, dairy, and meat), stearic acid (18:0; meat and dairy), myristic acid (14:0; dairy and tropical oil) and lauric acid (12:0; dairy and tropical oil) (U.S. Department of Agriculture, ARS. Nutrient Intakes from Food and Beverages: Mean Amounts Consumed per Individual, by Gender and Age, in the United States, What We Eat in America, NHANES 2011-2012, available at www.ars.usda.gov/nea/bhnrc/fsrg [Accessed February 8, 2018]). These SFA, excluding stearic acid, have been associated with increases in TC, LDL-C, and HDL-C levels, where myristic acid exhibited the most potent cholesterol-raising effect (37-39). A meta-analysis of 60 controlled trials by Mensink et al. reported an increase in LDL-C and HDL-C concentrations by isocaloric replacement of carbohydrates with all types of SFA, excluding stearic acid (38). Myristic and palmitic acids increased LDL-C and HDL-C levels to a similar extent without significantly altering the TC/HDL-C ratio, whereas lauric acid had the largest LDL-C- and HDL-C-raising effect leading to a decrease in TC/HDL-C ratio (38). A 2016 meta-regression analysis by Mensink et al., with a goal of informing the development of updated WHO recommendations on SFA intake, determined the effects on blood lipids of replacing

carbohydrates with commonly consumed individual SFA (40). Compared with carbohydrates, an increased intake of lauric, myristic, or palmitic acid raised TC, LDL-C and HDL-C levels, and lowered TG levels, while increased intake of stearic acid did not alter these values. Lauric acid alone reduced the TC/HDL-C and LDL-C/HDL-C ratios compared with carbohydrates (40). These findings are in line with those reported in an earlier review summarizing evidence from RCTs and prospective cohort studies. Taking the carbohydrate consumption as the reference, lauric, myristic and palmitic acids increased TC and LDL-C concentrations, whereas stearic acid did not (37). Both LDL-C- and HDL-C-raising effects of SFA were dependent on chain-length as these effects decreased as chain-lengths increased. In line with previous observations, the TC/HDL-C ratio was not significantly affected by myristic or palmitic acid consumption, but was significantly decreased by lauric acid consumption (37). Karupaiah et al., found that postprandial HDL-C response differed between subjects consuming test meals similar in fat content (~31%) but with a varying content of SFA (41). Compared to a stearic acid-rich meal, a lauric and myristic acid-rich or a palmitic acid-rich meal significantly increased the HDL-C concentration and the HDL-C area under the curve was elevated by 14% and 8%, respectively. Overall, these reports indicate heterogeneity across individual SFA with regard to potency to alter blood lipids. The consistent lack of association between stearic acid and cholesterol concentration has been linked to a slower and/or less efficient absorption as well as desaturation of stearic acid to oleic acid (42). Stearic acid content of beef and pork/lamb fat is ~20% and ~10-15%, respectively. It is worth noting that there are other factors with a potential to modulate the effects of SFA on blood lipids/lipoproteins and related health outcomes. These factors may include sex, lifestyle factors such as overall dietary composition and physical activity, clinical conditions such as obesity, insulin resistance and hypertriglyceridemia, as well as genetic factors such as those associated with metabolic syndrome and obesity. The 2017 AHA Presidential Advisory on Dietary Fats and CVD concluded that differences in the effects of the individual SFA are small and should not affect current dietary recommendations to lower saturated fat intake (43).

Effects of Dietary Cholesterol on Plasma Lipids and Lipoproteins

Some dietary guidelines recommend to limit dietary cholesterol intake <200 mg/day or <300 mg/day. Five decades ago, AHA included an initial recommendation to restrict dietary cholesterol to <300 mg/day to its dietary guideline intended for people who are at high risk for heart disease (American Heart Association 1968 Diet and heart Disease Risk. Dallas: American Heart Association). Specifically, egg consumption was limited to three whole eggs per week. This recommendation was based on several lines of available scientific evidence at that time. Early animal experiments conducted in rabbits fed with milk and egg yolks (44) or pure cholesterol (45-47) showed a hypercholesterolemia and severe atherosclerosis. Subsequent nonhuman primate experiments noted that feeding egg yolks to rhesus monkeys elevated the plasma cholesterol level, which led to development of atherosclerotic lesions similar to that of human atherosclerotic plaque after months of feeding (48). Reversibility of atherosclerosis was investigated in egg-yolk-induced hypercholesterolemic rhesus monkeys (48). Feeding monkeys with cholesterol-free diets resulted in regression of atherosclerosis as demonstrated by significant reductions in occlusions of coronary arteries and in cholesterol content of

atherosclerotic plaques. Epidemiological observations have reported an association between dietary cholesterol intake and CHD risk (49-53) and feeding with a high-cholesterol diet increased serum cholesterol concentrations (54-56). Subsequent metabolic experiments in human subjects have documented an effect of dietary cholesterol on plasma TC and LDL-C levels (57-60).

Research over the last a few decades, however, has produced significant amount of data supporting a minimal or no effect of dietary cholesterol on blood cholesterol level or CHD risk. The 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk concluded that there is insufficient evidence to determine whether lowering dietary cholesterol reduces LDL-C levels (19). The recent 2015 to 2020 edition of Dietary Guidelines for Americans contains no recommendation for dietary cholesterol intake (28).

In addition to an early study by Keys et al. (61), other feeding experiments of human subjects have reported no association between dietary and serum cholesterol concentrations (62). Analyses of epidemiological data have failed to find a significant impact on CHD risk by dietary cholesterol within populations (63-67). As reviewed by Ravnskov (68), in 11 reports from the prospective and retrospective epidemiological studies, dietary cholesterol was not different between cases and controls. Notably, in many studies HDL-C level was increased, therefore, LDL-C/HDL-C ratio was not altered (59,69-71). Data also indicate that cholesterol feeding does not alter number of LDL particles – instead it increases cholesterol content of these particles leading to formation of large buoyant LDL (72). Other nutritional components of a food, such as fats, can modulate the effects of dietary cholesterol on plasma levels. Particularly, SFA is a major factor and acts synergistically with dietary cholesterol to induce hypercholesterolemia (73). Addressing this topic, Keys et al. (74) developed an equation to predict changes in plasma cholesterol concentration, taking into account dietary cholesterol and saturated and unsaturated fats, while others have used a cholesterol/saturated fat index (75). Using the Keys equation, a meta-analysis of three RCTs determined that 15-20% of the total reduction in serum cholesterol was accounted for by decreased dietary cholesterol intake (43). Dietary cholesterol, however, was not associated with CHD risk among >80,000 nurses (65) and 43,000 male health care professionals (66) after taking energy, PUFA, *trans* fats and SFA into account. Similarly, significant associations between dietary cholesterol and CHD risk were abolished after covariates, including SFA, were taken into account (51,76). A 2013 meta-analysis of prospective cohort studies found no evidence of an association between egg consumption and risk of CHD or stroke (77). A similar 2016 meta-analysis of prospective cohort studies concluded that up to one egg daily may even contribute to a decreased risk of total stroke and that daily egg intake was not associated with CHD risk (78).

It should be noted that although overall effects of dietary cholesterol on serum cholesterol within/across populations maybe weak, the effects can be substantial for certain individuals. Thus, a considerable interindividual variation in response to a diet high in cholesterol has been observed. It is postulated that approximately 15-25% of the population respond to dietary cholesterol in a significant manner (i.e., sensitive or hyper-responders), while the majority

respond minimally (i.e., non-sensitive or hypo-responders) (79). As reviewed by McNamara et al. (80), an intake of 100 mg/day dietary cholesterol leads to a 3-fold difference in LDL-C concentration between hyper- and hypo-responders [an increase of 2.84 mg/dL (0.07mmol/L) vs. 0.76 mg/dL (0.02 mmol/L), respectively]. However, HDL-C appears to be less affected by this phenomenon (80). In addition, an individual's body weight and insulin resistance status may influence the effects of dietary cholesterol on plasma lipids and lipoproteins (81). An increase in non-HDL-C concentration was observed in lean and insulin sensitive individuals but not in lean and insulin resistant or obese and insulin resistant individuals after a 4-wk intervention with four eggs per day (82). Overall, individual dietary recommendation with consideration of differences in response to dietary cholesterol intake as well as genetic variability influencing cholesterol metabolism is important to achieving prevention and treatment goals for hypercholesterolemia and to reducing CHD risk.

Effects of Saturated Versus Monounsaturated and Polyunsaturated Fatty Acids and Carbohydrates on Plasma Lipids and Lipoproteins

The strategy of reducing dietary saturated fat intake raises a critical question about what kinds of nutrients should be used to replace saturated fat, and several major macronutrients, such as carbohydrates and *cis*-unsaturated fatty acids, including PUFA and MUFA, have been tested in many investigations. It is now increasingly appreciated that the effects on lipid profile and CVD risk of replacing SFA is highly dependent on whether it is being replaced with PUFA, MUFA, or carbohydrates (complex whole grain-rich vs. simple sugar-rich).

REPLACEMENT OF DIETARY SATURATED FAT WITH POLYUNSATURATED FATTY ACIDS

Replacement of energy from saturated fat with PUFA has been shown to decrease TC and LDL-C, with a concomitant decrease in HDL-C (83). Meta-analyses of short-term controlled dietary trials have shown a favorable influence of PUFA on the ratio of atherogenic vs. atheroprotective lipoproteins. The HDL-C/LDL-C ratio was increased due to a larger decrease in LDL-C than HDL-C (84), and the TC/HDL-C ratio was decreased (38). Interestingly, it has been noted that the availability and/or content of PUFA may modulate the effects of saturated fat on plasma lipids and lipoproteins, such that saturated fat may only increase LDL-C if the PUFA intake, specifically linoleic acid, falls below a threshold level of approximately 5% of energy (85,86). Thus, TC, LDL-C and apoB levels were not different between women who consumed diets high and low in saturated fat, but with similar ratios of polyunsaturated to saturated fat (87). Among Japanese subjects, the ratio of polyunsaturated to saturated fat was inversely associated with TC and LDL-C, but not with HDL-C, TG, and hemoglobin A1c (HbA_{1c}) (88). A reduced LDL-C synthesis rate (89,90) and/or increased clearance rate (91) may underlie observed reductions in LDL-C when PUFA is substituted for saturated fat. In addition, in nonhuman primates, replacement of dietary saturated fat with PUFA (92) but not with MUFA (93) was shown to reduce coronary artery atherosclerosis. It was projected that the replacement of saturated fat with PUFA, through its favorable effects on TC, LDL-C, and TC/HDL-C ratio, can provide about 10% decrease in coronary risk for each 5% energy substitution (37,94). However,

it could be postulated that the actual effects on overall CHD risk may be greater, considering that PUFA reduces inflammation and improves insulin resistance (95). Furthermore, the amount of cholesterol consumed in the diet modulates the effects of saturated fat, as the increase in LDL-C at lower intakes of cholesterol was minimal compared to the substantial increase of LDL-C at higher intakes of cholesterol (73).

The 2017 AHA Presidential Advisory on Dietary Fats and CVD identified four “core” trials, which met their evaluation criteria for design, execution, and adherence, for the beneficial effects of replacing SFA with PUFA (43). The 1st trial, the Wadsworth Hospital and VA Center in Los Angeles, reported a 13% reduction in serum cholesterol of replacing SFA with PUFA (96). The average duration was 8 years, and the participants were men with a mean age of 65 years. In the 2nd trial, the Oslo Diet-Heart Study, a PUFA-rich diet was associated with a 14% reduction in serum cholesterol among men and the effects were sustained throughout the 5-year trial (97). The 3rd trial, the British Medical Research Council, showed a 16% reduction in serum cholesterol in men after MI by replacing animal fat with soybean oil (98). In the 4th trial, the Finnish Mental Hospital Study, serum cholesterol was 14% lower on the high PUFA diet than on the high SFA diet in men and women (99) (100). The advisory group further performed a mixed-effects meta-analysis of these four core trials, all of which were conducted in the 1960s, and estimated a 29% reduction in CHD by lowering SFA and replacing it with vegetable oil (primarily soybean oil) rich in PUFA (43). A 2016 systematic review and meta-regression analysis of data in 84 RCTs showed that replacement of 1% total daily calories from SFA with PUFA, MUFA or carbohydrates lowers LDL-C by 2.1 mg/dL, 1.6 mg/dL, and 1.3 mg/dL, respectively (40).

REPLACEMENT OF SATURATED FAT WITH MONOUNSATURATED FATTY ACIDS

In a meta-analysis of short-term controlled dietary trials, replacement of saturated fat with MUFA was associated with decreases in TC and LDL-C (84). Although these effects may be of a lesser magnitude than those associated with PUFA, they were of a similar magnitude to those associated with carbohydrates (84,101,102). Comparing the effects of replacement of 7% energy from saturated fat in the average American diet (AAD, 36% energy from fat) with either MUFA or carbohydrates (primarily complex), Berglund at el., showed that both diets were able to reduce TC, LDL-C, HDL-C, ApoB, and ApoA-1 concentrations (103). In this 7-wk randomized, double-blind, cross-over study among subjects with metabolic risk factors, both regimens reduced LDL-C equivalent to 6 to 7%, consistent with previous observations (104,105). Triglycerides were significantly elevated with the carbohydrate diet, but tended to be lower with the MUFA diet. Reductions in HDL-C or ApoA-1 were of a lesser magnitude with the MUFA diet vs. the carbohydrate diet. In addition, plasma lipoprotein(a), Lp(a), concentrations were elevated with both diets, with a slightly larger increase observed for the carbohydrate diet (103). Studying exclusively the effects of dietary interventions on Lp(a) concentration, a recent randomized feeding study reported that diets rich in unsaturated fat (MUFA 21% and PUFA 10% of energy) increased Lp(a) levels less than diets rich in carbohydrate or protein, with greater changes in African-Americans than Caucasians (106). Overall, these findings suggest that replacement of

saturated fat with MUFA is a preferable regimen when compared to strategies using carbohydrate (or protein) as a replacement.

Substitution of MUFA for PUFA increased TG levels (107-109). In line with these findings, a meta-analysis reported a modest but consistent lower TG level on the diets high in PUFA vs. high in MUFA (110). The latter meta-analysis compared the effects of MUFA or PUFA consumed in oil forms on serum lipid levels focusing on studies with at least two intervention diets, differing in MUFA and PUFA content, but otherwise similar in total and saturated fat, fiber, and dietary cholesterol. There were no significant differences in TC, LDL-C, or HDL-C. Replacement of saturated fat with either MUFA or PUFA led to significant decreases in TC and LDL-C, and the pooled effect sizes were comparable for either type of unsaturated fatty acids [≈0.65 mmol/L (25 mg/dL) relative to the saturated fat diet] (110). Neither type of unsaturated fat significantly changed HDL-C or TG levels relative to the high-saturated fat diets. It was noted that any dietary recommendations for the use of PUFA or MUFA in preference to the other should be based on outcomes other than cholesterol concentrations. A recent meta-analysis of long-term, randomized, controlled dietary intervention trials comparing dietary regimens with high (>12%) vs. low (≤12%) amount of MUFA reported no significant differences in changes of TC, LDL-C, HDL-C, and TG (111).

REPLACEMENT OF SATURATED FAT WITH CARBOHYDRATES

The findings related to replacement of energy from saturated fat with carbohydrates have been much more complex. Carbohydrate foods differ substantially in their quantitative and qualitative features with regard to micronutrients, phytochemicals, fibers, and other bioactive substances, which could in turn have differential effects on plasma lipids and CHD risk.

Substitution of SFA with carbohydrates was associated with lower TC, LDL-C, and HDL-C, and higher TG (112). However, the TC/HDL-C ratio was not altered due to a similar magnitude of changes in TC and HDL-C concentrations (38). On the contrary, a large-scale randomized clinical trial (RCT) (the Women's Health Initiative Dietary Modification Trial) did not find evidence of beneficial (or adverse) effects on plasma lipids by exchanging 7-8% saturated fat with complex carbohydrates (113). In this study, 48,835 postmenopausal women (50–79 years of age) were randomized to either a low-fat (20% of calories) intervention or to a comparison group, and a subset with blood lipids (n=2,730) was assessed for the effects of dietary carbohydrate changes on lipid and lipoprotein composition. SFA intake was lower in the intervention group vs. the control group (9.5 and 12.4%, respectively) and dietary carbohydrate levels were higher (53.9 and 45.9%, respectively). No differences were observed between groups in the incidence of fatal and nonfatal CHD and total CVD after 8.1 years, indicating no beneficial effect of a reduced fat diet (28.8 vs. 37.0% of calories as fat).

Among healthy subjects, replacement of saturated fat with carbohydrates resulted in reductions of TC and LDL-C across sex and ethnicity (114). In a randomized cross-over trial among subjects with a high prevalence of metabolic abnormalities, both regimens, replacing 7% of

energy from saturated fat with carbohydrate (primarily complex) or MUFA, resulted in significant decreases in TC, LDL-C, and HDL-C (103). Triglyceride concentrations tended to be lower with the MUFA diet, but were significantly higher with the high carbohydrate diet. Overall, replacement with MUFA was associated with lesser reductions in HDL-C and lesser increases in TG as well as in Lp(a) concentrations. Of note, the dietary lipid responses varied on the basis of baseline lipid profiles, but they did not differ by metabolic syndrome or insulin resistance status (103).

Mixed results have been reported in diabetic patients with respect to the effects of dietary carbohydrates on plasma lipids (115). Triglyceride levels were significantly decreased with a carbohydrate restricted diet compared to a diet high in carbohydrates (50%–55% of energy from carbohydrates) (116,117). The effects of carbohydrate restriction on LDL-C and HDL-C appear to be largely modulated by the dietary fatty acid distribution (118). Under weight-stable conditions, low-carbohydrate diets led to reductions in TC/HDL-C, apoB and small dense LDL particles, with comparable magnitude of changes to that of achieved by weight loss (without restriction of carbohydrate intake) (119,120). A recent systematic analysis of 17 clinical trials among obese subjects reported that low-carbohydrate diets were associated with significant decreases in TG and increases in HDL-C, without impacting LDL-C (121).

Carbohydrates and Atherogenic Dyslipidemia

In recent years, increasing attention has been paid to the dietary modulation of “atherogenic dyslipidemia”, characterized by a higher proportion of small dense LDL particles, reduced concentrations of HDL-C and increased concentrations of TG (122). Individuals with obesity, the metabolic syndrome, insulin resistance and/or type 2 diabetes mellitus often exhibit atherogenic dyslipidemia and are at increased risk for CVD (123,124). Studies replacing saturated fat with carbohydrates have investigated the impact of carbohydrate intake on LDL particle size, which has been associated with CVD endpoints (125-129). To aid CVD risk stratification of patients, some lipoprotein assays have established cut-off points for LDL particle size: a particle size of >25.5 nm as measured by gradient gel electrophoresis is defined as Pattern A (normal) and a particle size of <25.5 nm is defined as Pattern B (atherogenic) (130,131). Individuals with pattern B have a higher proportion of small dense LDL particles, and thus more likely to have atherogenic dyslipidemia.

The amount of dietary carbohydrates was associated with a decrease in LDL particle size and an increase in LDL density, contributing to the atherogenic dyslipidemia (132). In a crossover study among healthy middle-aged men, a 6-wk intervention with a low-fat and high-carbohydrate (LFHC) diet resulted in significantly elevated concentrations of TG and small/very small LDL particles with a lower concentration of HDL-C as compared to a high-fat low-carbohydrate (HFLC) diet (133). Of note, proportions of saturated vs. unsaturated fat (1:1) and simple vs. complex carbohydrates (1:1) were kept the same in these studies. Additionally, many individuals who were pattern A on the HFLC diet became pattern B when consumed LFHC diet. All individuals who had pattern B on HFLC diet did not change on LFHC diet.

Furthermore, individuals who consistently had pattern A on both HFLC and LFHC diets underwent a follow up study with a very low-fat diet (10% of calories from fat with replacement with carbohydrates) (134). One third of these individuals converted to pattern B on this diet. Thus, it was suggested that reduced fat consumption replaced with an increased intake of carbohydrates modifies lipid and lipoprotein profiles towards atherogenic dyslipidemia. On the other hand, reductions in dietary carbohydrate, even in the context of a diet high in saturated fat, have been associated with increases in large and medium LDL particles, and decreases in small, dense LDL particles (135). In a study among overweight men, where the differences between higher (54% of calories from carbohydrate, 1:1 simple: complex) vs. lower (39%, 1:1) carbohydrate diet were made up with protein calories (not fat), the subjects had a higher prevalence of pattern B when on the high-carbohydrate diet. These observations indicate that dietary carbohydrates may be a driving force for atherogenic dyslipidemia.

Another study in overweight men provided a more detailed view with respect to the effects of varying carbohydrates and saturated fat, as well as weight loss, on lipid profiles (135). Under weight-maintenance phase, the subjects on low-carbohydrate diets experienced significant decreases in their TG and small/very small LDL particle concentrations, whereas the subjects on the higher-carbohydrate diet showed only modest changes. In contrast, under the weight-loss phase, subjects on higher-carbohydrate diet displayed larger decreases in TG and small/very small LDL particle concentrations than did those on the lower-carbohydrate diet, and caught up with the subjects on the lower-carbohydrate diet by the end of the study (a catch-up phenomenon). In this study, comparing low-carbohydrate diets with a high vs. a low saturated fat content, changes in TG, small LDL particles, or prevalence of pattern B, both underweight-maintenance and weight-loss phases, did not differ significantly. In line with these findings, diets high in saturated fat (38% of calories from fat of which 20% of calories from saturated fat) or high in MUFA (38% of calories from fat of which 22% of calories form MUFA) yielded no significant differences in TG, small LDL particles, or prevalence of pattern B (136). In contrast, when compared to a high-carbohydrate diet (30% of calories from fat, 55% of calories from carbohydrate) both high-fat diets resulted in larger LDL sizes, with one third of subjects converting to pattern B from pattern A on the high-carbohydrate diet. Finally, in the Framingham Heart Study, after multivariate adjustments for carbohydrate intake and a variety of other confounders, there were no differences in TG or LDL size across various fat contents (total, saturated, MUFA, or PUFA) (137).

A recent 4-wk intervention study among 63 healthy individuals found a significantly smaller LDL peak particle size after a LFHC diet compared to a HFLC diet (138). In addition, the LFHC diet increased plasma concentrations of Lp(a), oxidized phospholipid (OxPL)/apoB ratio, and OxPL-apo(a) compared to the HFLC diet. Changes in Lp(a) were strongly correlated with changes in OxPL/apoB, decreases in medium LDL particles, and increases in very small LDL particles (138). A 9-month intervention study in overweight and obese adults reported significantly increased LDL particle size after a low-carbohydrate diet, whereas there was no difference after a low-fat diet (139). Of note the change in body weight was similar between these two groups. It is likely that among overweight/obese individuals, when LDL size is already

decreased, no further decrease can be induced by a low-fat diet. A Mediterranean-style diet with reduced energy intake from carbohydrate and fat (but with increases in MUFA intake) and increased energy intake from protein has been shown to reduce small LDL (140). In addition, the ratio of large HDL to small HDL particles was increased and ApoB, OxLDL and Lp(a) concentrations were reduced after a 12-wk of intervention.

Overall, these findings suggest that dietary fat content may not have a major impact on atherogenic dyslipidemia, that carbohydrate metabolism impacts LDL particle quality rather than its quantity and that diets low in carbohydrate may help to improve LDL quality. However, lower-fat and higher-carbohydrate diets, compared to higher-fat and lower-carbohydrate diets, may induce greater reductions in LDL-C concentrations (particularly in individuals starting with pattern B). Therefore, beneficial effects of a high or a low carbohydrate diet on cardiovascular health remain to be clarified. It is likely that dietary strategies tailored to meet individual's need with regard to improving overall lipid profile with consideration for the personal preference for food choice over the long term and/or the individual metabolic and genetic environment have the promise to bring the most sustained and beneficial effects.

DIETARY SUGARS, GLYCEMIC INDE, GLYCEMIC LOAD, AND ATHEROGENIC DYSLIPIDEMIA

Dietary sugar is a major source of carbohydrates, and research focused on sugar consumption has provided much evidence supporting a role of sugar in the development of cardiometabolic disease. Different kinds of sugar impact differentially on the lipid profile and its contribution to atherogenic dyslipidemia. Fructose is known to increase TG levels and impair insulin sensitivity, and has been shown, in several recent studies, to more adversely impact LDL particle subclass profile than glucose. In a 10-wk study among overweight and obese individuals, indices of postprandial TG (23-h area under the curve, TG exposure and postprandial peak, but not fasting TG) increased after fructose, but not after glucose intake (141). Of note, fructose also increased small dense LDL particles. High fructose corn syrup (HFCS) has become a major source of fructose intake, and a recent study investigated whether there are differences in the lipid profile after consumptions of HFCS, glucose, or fructose alone (142). In young healthy individuals, a 2-wk intervention with 25% energy requirements as HFCS-sweetened beverages resulted in significant increases of fasting LDL-C, non-HDL-C, apoB, postprandial TG, remnant cholesterol and TG, as well as in small dense LDL particles. These changes were comparable to the ones seen with fructose, but were greater than those seen with glucose (142). In a 3-wk RCT of healthy young men, LDL particle size was decreased compared with baseline after consumption of a moderate amount of fructose or sucrose (80 g/day) and a shift towards a more atherogenic profile in the LDL subclass distribution was observed (143). A consumption of a lower amount of fructose (40 g/day) was also associated with similar changes. In addition, among overweight schoolchildren, fructose intake predicted LDL particle size (144).

Carbohydrate containing foods can differ substantially in their ability to impact postprandial glucose concentrations, and this effect can be quantified by "glycemic index" (GI) (145) or

“glycemic load” (GL) (146). Consumption of carbohydrates with a higher GI was associated with an increased plasma TG concentration in a large observational study, and this observation was independent of age, BMI, exercise, and the intake of other macronutrients (147). A 2008 meta-analysis of observational studies reported an association between the consumption of lower GI foods and lower TG and higher HDL-C concentrations (148). It was estimated that replacement of high GI foods for low GI foods can result 15% to 25% reductions in TG concentrations (149). A high GI was associated with an unfavorable lipoprotein subclass profile as determined by a nuclear magnetic resonance spectroscopy (150). Using the GI/GL classification system, the effects of low vs. high GI diets on cardiovascular risk factors were evaluated in a meta-analysis of RCTs conducted between 1981 and 2003 (151). Low GI diets, compared to high GI diets, were associated with significant improvements in markers of glycemic controls and TC concentration, but there were no associations with HDL-C, LDL-C, and TG concentrations, although a subgroup analysis in diabetic patients showed a non-significant trend towards a lower LDL-C concentration. A 2004 Cochrane meta-analysis of 21 RCTs among subjects with at least one major CVD risk factor or a CHD diagnosis, where subjects were provided either dietary instruction or food for a minimum of four weeks, concluded that there is no significant effect of the GI value of the diet on fasting glucose, insulin, HbA1c, HDL-C, and TG concentrations (152). However, low GI diets resulted in a modest decrease in LDL-C concentration (p=0.05) (152). In 2017, the same authors updated their analysis using data from 21 RCTs, of which the majority were newly added studies (153) and again found no evidence of a difference between low and high GI diets for TC, LDL-C, HDL-C, and triglycerides.

In contrast, a 2013 meta-analysis of RCTs comparing studies that supplied at least one meal per day with a high or low GI value found significant reductions in TC [-0.13 mmol/L (5 mg/dL), 27 trials, 1,441 participants] and LDL-C [-0.16 mmol/L (6.2 mg/dL), 23 trials, 1,281 participants] concentrations with low vs. high GI diets. Again, there was no evidence that a low GI diet was beneficial for HDL-C or TG concentrations (154). These inconsistent findings across meta-analyses of RCTs could be due to inclusion of studies with different study settings/designs with regard to the application of dietary interventions. It is important to distinguish between RCTs where participants were provided only dietary instructions to modify their dietary GI values, and those where some or all foods (i.e., controlled-feeding trials) were supplied to the participants. To address these issues, Kristo et al. recently attempted to summarize the effects of diets differing in GI/GL on cardiovascular risk factors by focusing on only randomized controlled-feeding trials where all foods and beverages were provided to participants (155). Two cross-over studies (designed to maintain weight) reported contradictory results (156,157). One study found significant increases (156) and the other found significant decreases (157) in TC, LDL-C and HDL-C with the low vs. high GI diet (155). In three other parallel studies (designed for weight loss) (158-160), TC, LDL-C, VLDL-C, and TG concentrations were not affected by the GI value of diets. It was concluded that it is premature to use GI/GL values of the diets in formulating dietary recommendations (155).

Studies by Stanhope et al. may provide more insights into the potential role and use of GI in cardiometabolic disease risk (161). The GI of fructose is 23 compared with 100 for glucose. In

their studies, the calculated relative GI of the baseline complex-carbohydrate diet, the high-glucose intervention diet, and the high-fructose intervention diet, consumed during the 24 h blood collections, was 64, 83, and 38, respectively (141,142,161). As expected, glucose and insulin excursions of the diets paralleled the GI, with exposure being highest on the glucose diet, intermediate on the complex-carbohydrate baseline diet, and lowest on the fructose diet. However, individuals consuming the high-fructose diets with the lowest GI index and glycemic exposure exhibited increased visceral abdominal adipose tissue and decreased insulin sensitivity (141), and increases of LDL, apoB, and postprandial TG (141,142). In contrast, when individuals consumed high-glucose diets, postprandial plasma glucose and insulin excursions increased substantially (141,142), however, insulin sensitivity (141) and postprandial TG exposure, LDL, and apoB remained unchanged (141,142), These findings underscore the importance of accurately assessing glucose and fructose content in study diets. The authors noted that dietary fructose may be an important contributor to the inconsistent reported effects of dietary GI on metabolic risk factors, and that this together with other differences (e.g., fiber content) between high and low GI diets, may underlie these inconsistent observations (161). It is likely that the fructose, and not the glucose, component of sucrose and HFCS is primarily responsible for their adverse metabolic effects (161).

Effects of Saturated Fat and Its Replacements on Coronary Heart Disease Risk

In 2009, a pooled analysis of 11 prospective cohort studies demonstrated a significant inverse association of PUFA with risk of coronary events and death for a 5% lower energy intake from SFA and a concomitant higher energy intake from PUFA (162). There was a modest but direct association of coronary events with replacement of the same amount of energy with carbohydrates and no association of MUFA with coronary risk. It was suggested that replacing SFA with PUFA rather than MUFA or carbohydrates prevents CHD over a wide range of intakes (162). Mozaffarian et al. (94), in their 2010 systematic review and meta-analysis of RCTs of more than 1-year duration, showed that saturated fat replaced with vegetable oil rich in *n-6* PUFA reduced CHD incidence, and that the stronger the saturated fat reduction the lower the CHD incident. In these trials, the average PUFA consumption was 15% of energy in the intervention diets and 5% of energy in the control diets. The overall pooled reduction in CHD incidence was 19% corresponding to 10% reduced risk per 5% energy of increased PUFA intake. Study duration was an independent predictor of risk reduction, with studies of longer duration showing greater benefits. Of the eight trails included in this meta-analysis, only three of the RCTs replaced saturated fat with solely *n-6* PUFA, whereas the other five RCTs used a mixture of *n-6* and *n-3* PUFA. In these latter trials, CHD incident was reduced by 22%.

A 2014 linoleic acid-focused meta-analysis of 13 prospective cohort studies reported a 15% lower risk of CHD events and a 21% lower risk of CHD deaths when comparing the highest category with the lowest category (163). A 5% of energy increment in linoleic acid intake replacing energy from SFA was associated with a 9% lower risk of CHD events and a 13% lower risk of CHD deaths. Thus, dietary linoleic acid intake is inversely associated with CHD risk

in a dose-response manner, providing support to current recommendations to replace SFA with PUFA for primary prevention of CHD.

In two large cohort studies (Nurses' Health Study and Health Professionals Follow-up Study) with a follow-up of 24 to 30 years, higher intakes of PUFAs and carbohydrates from whole grains were significantly associated with a lower risk of CHD (164). Replacing 5% of energy from SFA with equivalent energy from PUFAs, MUFAs, or whole-grain-carbohydrates was associated with a 25%, 15%, and 9% lower risk of CHD, respectively.

A 2010 meta-analysis of 21 prospective cohort studies using a random-effects model, which allows heterogeneity of variance between studies, reported no significant association of saturated fat intake with CHD, stroke, or CVD (165). Evaluation of the subset studies that adjusted for total energy, which has been shown to be relevant in evaluating nutrient-disease relations (166), yielded similar results. As the authors noted, due to insufficient information in the component studies with respect to dietary carbohydrates or PUFA, the meta-analysis did not asses the effects on CVD risk of replacing specific amount of saturated fat with either carbohydrate or PUFA. The meta-analysis stated that there is insufficient evidence from prospective epidemiological studies to conclude that dietary saturated fat is associated with an increased risk of CHD, stroke, or CVD.

A 2013 re-analysis of recovered data from 1960s and 1970s in the Sydney Diet Heart Study reported a higher risk of all-cause mortality, CVD mortality, and CHD in the high *n-6* PUFA group (15% of calories as PUFA) compared to the control group (no specific dietary instruction) (167). These findings contradict current evidence that *n-6* PUFA intake is associated with reduced CVD risk. In these studies, however, PUFA was supplied as safflower oil margarine to substitute for animal fats, which may contain *trans* fatty acids. *Trans* fatty acids significantly increase CHD risk, and were not evaluated in these studies.

Regarding *trans* fatty acids, a meta-analysis of four prospective cohort studies, reported that a reduction in intake of *trans* fatty acids equal to 2% of energy is associated with a 24% lower risk for CHD (21). *Trans* fatty acids originate from two independent dietary sources: industrially produced and naturally occurring (i.e., ruminant). Since the report on differences in the impact of both dietary sources in the Nurses' Health Study (168), data from intervention studies have become available (169-172). In 2014, a systematic review and meta-analysis of 13 RCTs assessed the impact of ruminant *trans* fatty acids intake on changes in cardiovascular risk factors (173). No relationship was seen between intake of ruminant *trans* fatty acids up to 4.19% of energy and TC/HDL-C or LDL-C/HDL-C ratios. A multivariate regression analysis adjusting for other dietary variables and subjects' baseline characteristics confirmed that doses of ruminant *trans* fatty acids did not significantly influence the changes in the lipid ratio. It was concluded that *trans* fatty acids from natural sources, up to 4.19% of energy intake, had no adverse effects on these CVD risk markers in healthy people.

In 2014, a systematic review and meta-analysis of data from long-term prospective observational studies of a broad range of both dietary and biomarker fatty acid (FA) measures in coronary disease was published (174). In 32 observational studies (~500,000 participants) of FA from dietary intake, the relative risks (RRs) for CHD were 1.03 for SFA, 1.00 for MUFA, 0.87 for long chain *n-3* PUFA, 0.98 for *n-6* PUFA, and 1.16 for *trans* fatty acids when the top and bottom tertiles were compared. In 17 observational studies (≈26,000 participants) of circulating FA biomarkers, the corresponding RRs for CHD were 1.06, 1.06, 0.84, 0.94, and 1.05, respectively. In 27 randomized, controlled trials (~100,000 participants) of FA supplementation, the RRs for CHD were 0.97 for α-linolenic acid, 0.94 for long-chain *n-3* PUFA, and 0.86 for *n-6* PUFA supplementations. The meta-analysis then concluded that current evidence does not clearly support cardiovascular guidelines that encourage high consumption of PUFA and low consumption of total SFA. There have been several post-publication numerical corrections, including RR estimates, participants' numbers, and events in the meta-analysis; although the authors noted that these corrections do not affect the main conclusions reported in the original article.

Another recent observational finding by Virtanen et al. in a population with a high SFA intake and high rates of CHD (Kuopio Ischemic Heart Disease Risk Factor Study, n=1,981 Finnish men, aged 42 to 60 years and free of CHD at baseline in 1984 to 1989) adds to the notion that SFA intake is not an independent risk factor for CHD and that PUFA provides protective effect against fatal CHD, whether replacing SFA, trans fat, or carbohydrates (175). With regard to MUFA, there was a positive association between MUFA intake and CHD risk, which as the authors noted warrants further investigations.

Numerous meta-analysis and comprehensive reviews(176-183) have evaluated the effects of marine –derived *n-3* PUFA EPA and DHA on primary and secondary prevention of CVD and all-cause mortality, with many reporting beneficial effects for the former but not for the latter. A 2012 systematic review of RCTs and large prospective cohort studies by the Agency for Health Research and Quality reported that EPA+DHA supplementation (0.27-6.0 g/day) reduced RRs of cardiac mortality by about 11% (179). In contrast, several other recent meta-analyses have failed to find evidence on the beneficial effects of EPA+DHA intake on CVD risk. A 2012 meta-analysis of RCTs challenged the research that demonstrates protective effect of *n-3* PUFA supplementation on CVD, by reporting no association between *n-3* PUFA intake and CVD risk (177). Another meta-analysis of RCTs in patients with a history of CVD did not find sufficient evidence of a secondary preventive effect of *n-3* PUFA supplementation against cardiovascular events (178).

A 2014 meta-analysis of 32 cohort studies (841,211 subjects) focused on MUFA reported an overall risk reduction of all-cause mortality (11%), cardiovascular mortality (12%), cardiovascular events (9%), and stroke (17%) when comparing the top vs. bottom third of MUFA, olive oil, oleic acid, and MUFA:SFA ratio (184). A subgroup analyses indicated significant associations between higher intakes of olive oil and reduced risk of all-cause mortality, cardiovascular events,

and stroke, whereas the MUFA subgroup analyses did not reveal any significant risk reduction (184).

A 2017 Presidential Advisory from the AHA concluded that lowering intake of SFA and replacing it with unsaturated fats, especially PUFA, will lower the incidence of CVD, through lowering of LDL-C, a cause of atherosclerosis (43). A 2017 systematic review reported that a high intake of SFA and *trans* fats is associated with an 8-13% higher total mortality (185). Replacement of SFA with any carbohydrates, PUFA or MUFA was associated with a lower total mortality, with PUFA being more effective than MUFA (19% vs. 11% reduction). With regard to CVD mortality, replacement of SFA with PUFA and fish oil, 5% total energy, lowered risk by ~28%. CHD events were found to be equally reduced by replacements with PUFA or MUFA. While replacement of SFA with high-quality carbohydrates (whole grains) reduces CHD events, its replacement with sugar/starch increases the events. PUFA replacement of SFA was the only strategy to show reductions in all three outcomes, i.e., all-cause mortality, CVD mortality, and CHD events (185).

Taken together, these findings underscore the complexity of assessing the effects of dietary interventions on cardiovascular risk and that there are likely many factors contributing to the variability in observations. These factors may include the presence of substantial heterogeneity in study settings and designs, publication biases, issues related with self-reported measures of dietary intakes as well as adherence measurements to study diet, a limited number of studies focused on certain types of diet or dietary composition, the approaches used to dissect the effects based on studies where substantially different approaches have been used, and many more. Nonetheless, well-designed, controlled, adequately powered, large-scale further studies should bring more insights into the role of dietary fat in coronary risk and coronary death, and will help to delineate controversies associated with the several decades old “the diet-heart theory”.

Efficacy of Dietary Interventions to Modify Blood Lipid Profile

Lifestyle changes recommended for those with high cholesterol levels include smoking cessation, limiting alcohol consumption, following a low saturated fat diet, avoiding *trans*-fat, increasing physical activity, and maintaining a healthy weight (186). Dietary advice given by health professionals in practice can provide only a modest decrease in cholesterol levels, and may be sufficient in the treatment of mildly elevated cholesterol (186).

In a systematic review of 19 RCTs, the efficacy of individualized dietary advice (to modify fat intake) to lower TC levels in free-living subjects and the efficacy of different dietary recommendations were evaluated (187). The percentage reduction in TC attributable to dietary advice after at least six months of intervention was 5.3%. Including both short- and long-term studies, the effect was 8.5% at 3 months and 5.5% at 12 months. Diets equivalent to the step 1 diet of the AHA (<30% of total energy intake as fat, with 8-10% as saturated fat; ratio of polyunsaturated to saturated fatty acid >1.0; cholesterol intake <300 mg/day, and energy intake

to achieve desirable body weight) (188) lowered cholesterol concentration by ~3%, and another 3% decrease was achieved with more intensive diets, equivalent to the step 2 diet of the AHA (<30% of total energy intake as fat, with 7% or less as saturated fat; ratio of polyunsaturated to saturated fatty acid >1.4; cholesterol intake <200 mg/day, and energy intake to achieve desirable body weight) (188). The latter diet was of similar efficacy to diets that aimed to lower total fat intake or to raise the polyunsaturated to saturated fatty acid ratio. It was concluded that individualized dietary advice for reducing cholesterol concentration is modestly effective in free-living subjects, and more intensive diets achieve a greater reduction in serum cholesterol concentration (187). Failure to comply fully with dietary recommendations is the likely explanation for this limited efficacy.

An updated 2013 Cochrane database systematic review analysis of 44 randomized studies (with at least three months duration, excluding trials to reduce weight or those involving dietary supplementations) assessed the effects of providing dietary advice to achieve sustained dietary changes or improved cardiovascular risk profile among healthy adults (189). Compared to no advice, dietary advice reduced TC by 0.15 mmol/L (5.8 mg/dL) and LDL-C by 0.16 mmol/L (6.2 mg/dL) after three to 24 months, while HDL-C and TG concentrations were unchanged. In addition, dietary advice increased fruit and vegetable intake by 1.18 servings/day and fiber intake by 6.5 g/day, with a 4.5% and 2.4% reduction in total and saturated dietary fat (as a percentage of total energy), respectively. It was concluded that dietary advice appears to be effective in bringing about modest beneficial changes in diet and cardiovascular risk factors over approximately 12 months, but longer-term effects are not known. A 2017 systematic review and meta-analysis of five RCTs in diabetic individuals compared individualized nutrition therapy with dietary advice (190). At short term (6 or 12 months), nutrition therapy compared with dietary advice was associated with a 0.17 mmol/L lower LDL-C level (6.6mg/dl), as well as a lower BMI and body weight, and improvements in HbA1c.

Modification of plasma lipid profile by low-fat dietary interventions was dependent on menopausal status of women. A 2014 meta-analysis of eight RCTs with a duration ≥4 wks among pre- and post-menopausal women reported significant reductions in TC [mean difference -0.49 mmol/L (18.9 mg/dL)], HDL-C [mean difference -0.12 mmol/L (4.6 mg/dL)] and LDL-C [mean difference -0.24 mmol/L (9.3 mg/dL)] by a low-fat diet intervention (191). Further subgroup analysis revealed that the low-fat diet was efficacious in reducing TC, HDL-C, and LDL-C in premenopausal women but not in postmenopausal women. A low-fat diet intervention, however, did not significantly alter TG concentration and TC/HDL-C ratio (191).

In contrast, in a strict environment, such as metabolic ward studies dietary changes can induce a greater reduction in cholesterol concentrations. Denke et al. evaluated the efficacy of the high-risk and population approach for cholesterol lowering by reviewing large trials of dietary intervention (≥150 participants) and smaller trials of angiographic assessment of the impact of diet on CHD (192). Two trials with an intensive individualized counseling achieved 75% to 80% of the cholesterol lowering predicted by metabolic ward studies and produced a 5% to 14% reduction in TC levels. Four studies among high-risk individuals exceeded predictions and

achieved a 4% to 17% reduction in TC levels. Similar efficacy was observed in six of the seven trials of diet for secondary prevention. Four trials employing the population approach achieved smaller but often significant reductions in TC levels of 1% to 11%. The effectiveness of dietary therapy was enhanced when individualized counseling was used, follow-up was maintained, and weight reduction was achieved.

A quantitative meta-analysis of metabolic ward studies (395 dietary experiments with median duration of one month, among 129 groups of individuals) demonstrated that replacing 60% of saturated fats by other fats and avoiding 60% of dietary cholesterol in typical British diets would reduce TC by about 0.8 mmol/L (31 mg/dL) (i.e., 10-15%), with four fifths of this reduction being in LDL-C (59). Specifically, isocaloric replacement of SFAs by complex carbohydrates for 10% of dietary calories resulted in TC falling by 0.52 mmol/L (20.1 mg/dL) and LDL-C falling by 0.36 mmol/L (13.9 mg/dL). Isocaloric replacement of complex carbohydrates by PUFAs for 5% of dietary calories resulted in TC falling by a further 0.13 mmol/L (5 mg/dL) and LDL-C falling by 0.11 mmol/L (4.2 mg/dL). Similar replacement of carbohydrates by MUFAs produced no significant effect on TC or LDL-C. Avoiding 200 mg/day dietary cholesterol further decreased TC by 0.13 mmol/L (5 mg/dL) and LDL-C by 0.10 mmol/L (3.9 mg/dL).

Table 2. KEY POINTS: DIET

1) Responses of blood lipids and lipoproteins to individual SFA intake are heterogeneous.
2) Cholesterol-raising effects of SFA depend on chain-length as these effects decrease as chain lengths increase.
3) SFA, excluding stearic acid, increase TC, LDL-C, and HDL-C levels, where myristic acid exhibits the most potent cholesterol-raising effect.
4) Overall effects of dietary cholesterol on blood cholesterol level are limited and modulated by other nutritional components.
5) There is a considerable interindividual variation in response to dietary cholesterol with some individuals (15-25%) demonstrating marked increases in LDL-C level.
6) Substitution of SFA with PUFA or MUFA decreases TC, LDL-C as well as HDL-C levels.
7) Substitution of SFA with carbohydrates lowers TC, LDL-C and HDL-C levels and increases triglyceride level.
8) High carbohydrate diets decrease LDL particle size and increase LDL density.

Abbreviations: SFA, saturated fatty acids, MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids;

PHYSICAL ACTIVITY AND EXERCISE

Historical Perspective

Founded on early observations on the relationship between occupational physical activity (PA) and chronic disease risk (e.g., CVD mortality), Jeremiah Morris et al. followed a large cohort of

London transport workers (age range: 35 -64 years) in 1949-1950 (193). They found that the sedentary bus drivers had higher rates of CVD mortality than their active counterparts, the conductors, and postulated that physically active work had a cardioprotective effect. This work was extended to postmen and postal clerks, where postmen who walked or cycled while delivering mail had much lower rates of heart disease than the postal clerks who had sedentary jobs (193). Further, Morris et al. documented a dose response for exercise by showing lower rates of CVD among postal workers whose jobs offered at least some PA compared to employees who spent most of the workday seated (193). It was posited that “men doing physically active work have a lower mortality from CHD in middle age than men in less active work.” In a 1966 article, Morris et al. reported a significant relationship between occupational PA and CVD, and that other CVD risk factors such as hypertension and blood lipids were reduced in physically active conductors compared with the sedentary drivers (194). Around the same time, in 1951, Ralph Paffenbarger et al. began an observational study of >3,000 San Francisco longshoremen (age range: 35-64 years), and followed them for 16 years (195). They found that the CVD death rate was significantly lower in the most active compared with sedentary workers. In 1975, Paffenbarger et al. examined repeated bouts of work activity in another cohort of >6,000 longshoremen, and reported that the longshoremen in the high expenditure per work shift group had lower age-adjusted rates for CVD compared with the other two groups (middle and low expenditure groups) (195). Numerous other studies have documented an inverse association between occupational PA and CVD risk (196-199).

In 1968, to test the hypothesis that PA outside the occupational domain would provide cardioprotective benefits, Morris et al. initiated a 3-year prospective study of executive-grade men in the UK (age range: 40-64 years). A vigorous leisure time PA was associated with a 33% reduction in RR of a CVD event, providing support for the role of vigorous PA in promoting cardiovascular health (200). Another study of Morris et al. with a 8-year follow-up demonstrated that individuals who engaged in vigorous leisure time PA had a lower rate of fatal CVD events and nonfatal CVD events when compared with sedentary counterparts (201). In 1978, Paffenbarger et al. in the College Alumni Heath Study, reported that individuals in the low energy-expenditure group had >60% increased risk of CVD regardless of other risk factors (202). A low PA when combined with another risk factor (i.e., smoking or hypertension) led to a 2.7 fold increase in RR; whereas combination of all 3 risk factors increased the RR to 7.7 (202). Over the past few decades, there has been a substantial accrual of epidemiological evidence on the inverse relationship between leisure time PA and CVD. A recent meta-analysis of 26 prospective cohort studies (513,472 individuals and 20,666 CHD events) with follow-ups of 4 to 25 years reported significant reductions in CVD mortality in both high and moderate levels of self-reported leisure time PA (203).

Physical Activity versus Different Modalities of Exercise

Although being used in the literature interchangeably, PA and exercise denote different concepts. According to the US Department of Health and Human Service and Centers for Disease Control and Prevention, “PA” refers to any bodily movement produced by skeletal

muscles that results in an expenditure of energy, which includes a broad range of occupational, leisure and daily activities; whereas “exercise” refers to planned or structured PA, performed for a reason, and can include aerobic exercise, resistance training or combined aerobic and resistance training (204).

PHYSICAL ACTIVITY

Physical Activity (PA) appears to impact CVD risk through beneficial effects on several factors, including adiposity, insulin sensitivity, glycemic control, type 2 diabetes incidence, blood pressure, blood lipids, endothelial function, hemostasis, and inflammatory defense systems (205). In the Women’s Health Study, these factors explained 59% of the observed inverse relation between PA and incident CVD over an 11-year follow-up period (206). Of note, among women, traditional and novel (Lp(a), apoA1, and B-100) blood lipids and lipoproteins contributed to lower risk by 19% and 16%, respectively. Inflammatory and hemostatic risk factors (CRP, fibrinogen, and soluble intercellular adhesion molecule-1) had the largest contribution to lower risk (33%), followed by blood pressure (27%), BMI (10%), and HbA_{1c}/diabetes (9%).

A 1999 report of the Nurses' Health Study examined the association between total PA and CHD events in >72,000 nurses (age range; 40 and 65 years) (207). There was a strong inverse gradient between PA energy expenditure and CHD events. When women were grouped in quintiles from inactive to highly active based on their self-reported PA patterns, the age-adjusted RR of a CHD event decreased in a stepwise fashion by 23%, 35%, 46%, and 54%, respectively. After multivariate adjustments (i.e., familial history, age, tobacco use, hormone replacement therapy, hypercholesterolemia, aspirin therapy, vitamin supplementation, and BMI), the association remained strong. This study demonstrated that women who walked vigorously for greater than 150 min/wk had a 35% reduction in CHD events compared with those who walked infrequently (207).

Aadahl et al. reported significant associations between self-reported 25-h PA and HDL-C (positive) or TG (negative) concentrations in a 3-year follow up study among previously sedentary 1,693 men and women aged 33–64 years (208). PA intervention was based on lifestyle consultations and subjects on lipid-lowering medications were excluded from analysis. A 5-year follow up study by the same investigators demonstrated significant improvements in TC, LDL-C, and TG among 4,039 participants aged 30–60 years, with an additional significant improvement in HDL-C seen only in men (209).

A 2017 pooled analysis of nine population-based cohorts (>37,000 adults) evaluated the associations between leisure-time PA, low HDL-C and mortality (210). Compared with those who met PA guidelines (≥150 min/wk of moderate-intensity PA, ≥75 min/wk of vigorous-intensity PA, or equivalent combinations) and whose HDL-C was normal (ref group), all-cause mortality risk was not elevated in those who met PA guidelines and whose HDL-C was low. In contrast, compared with the ref group, all-cause mortality risk was elevated in those who did not meet PA guidelines and whose HDL-C was either normal or low. CVD mortality hazard ratios were

similar, although confidence intervals were wider. These findings support the notion that leisure-time PA be recommended in those with low HDL-C who may be resistant to the HDL-raising effect of exercise training.

A community intervention trial among Spanish adults (mean age: 65 years; 77% women) assessed the short- and medium-term effectiveness of nine months of a supervised PA program (211). The intervention consisted of 120 min/wk walking (396 METs/min/wk) and sociocultural gathering once a month. At the end of the study, TC (-10.1 mg/dL) and LDL-C (-9.1 mg/dL) levels and systolic BP (-6.6 mmHg) were reduced significantly in the intervention group relative to the control group. At 2 yrs after the intervention, the incidence of adverse CVD events was significantly lower (3% vs. 11%) and the adherence to regular PA was higher (73% vs. 27%) in the intervention vs. the control group.

A 2017 systematic review and meta-analysis of RCTs (≥12 months) among adults without impaired glucose tolerance or diabetes estimated the effects of lifestyle interventions, involving PA, dietary, or combined strategies on CVD risk factors (212). Compared to usual care, lifestyle interventions achieved significant improvements in TC (-0.10 mmol/L) (3.9mg/dl), LDL-C (-0.09 mmol/L) (3.5mg/dl), HDL-C (0.03 mmol/L) (1.2mg/dl) and TG (-0.08 mmol/L) (7mg/dl) as well as BP. Combined strategies had greater and significant effects on blood lipid profile than PA alone strategy. The authors noted that this finding may be related to methodological shortcomings in exercise-only interventions such as low adherence, insufficient exercise volume or length of intervention (212). In addition, evidence suggests that it may take up to two years for a previously sedentary obese individual to attain enough volume of exercise to modify risk factors.

The potential associations with CVD risk factors of reallocating sedentary time in long bouts to sedentary time in non-bouts, light-intensity PA and moderate- to vigorous-intensity PA were evaluated in a cohort of pre-diabetic/diabetic individuals (213). Reallocation of sedentary time in bouts/non-bouts to moderate- to vigorous-intensity PA, but not to light-intensity PA, was associated with higher HDL-C levels. In addition, waist circumference and BMI were decreased. A recent small study among inactive older women with hypertriglyceridemia compared the effects of different patterns of walking on PP TG levels (214). Compared to the control regimen (8h sitting), continuous walking for 30 min in the morning or repeated short bouts over 8h reduced iAUC of PP TG by ~35%.

AEROBIC EXERCISE

Aerobic exercise training (AET) includes cardiorespiratory endurance exercises such as jogging, running, and cycling (204). A 6-month AET intervention, which progressed from 50 to 85 % of maximum aerobic power for 20–60 min 3 times/wk resulted in significant decreases in TC and the TC/HDL-C ratio (215). In a 16-wk shorter duration study of young women, LeMura et al. found significant reductions in TG and increases in HDL-C following a progressive training protocol (3 times/wk at 70–75 % HR_{max} for 30 min for the first 8 weeks, which progressed, thereafter, to 4 times/wk at 85 % HR_{max} for 45 min) (216).

A 2001 review article examined the effects of AET on blood lipids in exercise training intervention trials of more than 12 wks (217). A total of 51 studies, including 28 RCTs, were analyzed (~4,700 participants). A marked inconsistency was observed in responsiveness of blood lipids, with the most commonly observed change being an increase in HDL-C and with a less frequent reduction in TC, LDL-C, and TG concentrations. In training groups (61 groups, involving ~2,200 subjects) in which diet was held constant, the exercise-induced change in HDL-C ranged from a decrease of 5.8% to an increase of about 25%, with a mean increase of 4.6%. The increase in HDL-C with AET was inversely associated with its baseline level, but there were no significant associations with age, sex, weekly volume of exercise, or with exercise-induced changes in body weight or peak oxygen effect (VO_{2max}). Exercise training in the absence of simultaneous dietary interventions resulted in mean reductions in TG, LDL-C, and TC of 3.7%, 5.0%, and 1.0% ($p>0.05$), respectively. Men generally had a greater reduction in TG levels than women. It was concluded that moderate- to hard-intensity AET inconsistently results in an improvement in the blood lipid profile, but that the data was insufficient to establish dose-response relationships.

In 2001, while reviewing 51 studies on PA interventions, Kesaniemi et al. reported a mean increase of 4.6 % in HDL-C (218). The effects on LDL-C and TG were reported as being inconsistent. It was concluded that the most likely PA-induced improvement in the lipid profile is an increase in HDL-C concentrations. This finding was supported by Banz et al., who reported a 13% increase in HDL-C following a 10-wk AET (219). In this study, HDL-C was the only component of the lipid profile that improved by the intervention.

A 2002 RCT by Kraus et al. among sedentary, overweight women and men with mild to moderate dyslipidemia (n=111, 8 months duration) compared the effects of amount and intensity of exercise on blood lipid profile (220). All three AET exercise groups ("high-amount/high-intensity", "low-amount/high-intensity", and "low-amount/moderate intensity") experienced improvements in blood lipid profile compared to controls (after excluding subjects with significant weight reductions). Of note, there were no marked differences in the effects between the two "low-amount" exercise groups, whereas more pronounced effects for virtually all studied variables were seen in the "high-amount" exercise group. The latter group expended energy equivalent of jogging 17–18 miles/wk compared to the "low-amount/high-intensity" and "low-amount/moderate-intensity" groups, who expended the equivalent of jogging or walking 11 miles/wk, respectively. Thus, the "high-amount" exercise reduced LDL, IDL, and small LDL particles and increased the median size of LDL particles and HDL-C concentrations. All types of exercises had beneficial effects on TG and size of VLDL particles. It appears that the effects depend on the amount rather than the intensity of exercise training. In line with these findings, Nybo et al. comparing a prolonged (150 min/wk) AET protocol with an intense interval running protocol (40 min/wk) reported no improvements in the lipid profile with the latter intervention among previously untrained individuals (221). The TC/HDL-C ratio was the only component of the lipid profile that improved significantly by the prolonged protocol. The authors suggested that the training volume, as opposed to the training intensity, is the key to improving the lipid profile,

and that there may be a relationship between body fat (which decreased only in the prolonged exercise group) and cholesterol levels, whereby a volume sufficient to elicit changes in fat mass is required to favorably alter the lipid profile.

While controlling the exercise volume (equal energy expenditure, i.e. three 400 kcal sessions/wk, 24 wks duration), O'Donovan et al. assessed the effects of exercise intensity in 64 previously sedentary men (222). Significant improvements in blood lipid profile were reported in the high-intensity, but not in the moderate-intensity exercise group, with a significant decrease in TC, LDL-C and non-HDL-C concentrations. These findings suggest that moderate-intensity exercise may be sufficient to increase HDL-C concentrations, but that a more intense exercise is needed to improve other components of the lipid profile, such as LDL-C or TG concentrations.

The effects of exercise or PA on blood lipid profile may differ between gender groups. Specifically, HDL-C increased significantly more in men than in women (209,223) and men generally experienced greater reductions in TG concentrations than women (217). However, underlying mechanisms of these gender-specific differences as well as overall mechanisms by which exercise exerts its effects on blood lipids have not been fully delineated. The mechanisms may include reductions in hepatic lipase activity, increases in lipoprotein lipase activity (224) and lecithin-cholesterol acyltransferase (225), as well as increases in peak LDL particle diameter and HDL_2-mass (226,227). Among elderly women (70-87 years), a 10-wk AET intervention was associated with beneficial effects on blood lipid profile (228), suggesting that AET can help to ameliorate cardiometabolic burden also in this group.

In a 2009 systematic review Tambalis et al. considered the effectiveness of AET with different intensities (high and moderate) as well as types of other exercise in altering the blood lipids (229). The authors concluded that AET programs result in favorable effects only for high-intensity programs, with the most frequent alteration being an increase in the HDL-C. Reductions in TC, LDL-C and TG were seen less often.

RESISTANCE TRAINING

Resistance training (RT) refers to strength-developing exercise utilizing external resistance or one's own body weight (204). In sedentary healthy premenopausal women (n=24), Prabhakaran et al. investigated the effects of an intensive 14-wk RT program [3 times/wk, ~50 min/session at 85% of one repetition maximum (1 RM)] on the lipid profile (230). 1 RM is defined as the maximal load that can be lifted once for a given exercise. Compared to baseline values, TC, LDL-C and TC/HDL-C ratio decreased significantly, but no differences were seen in TG and HDL-C concentrations. In elderly women (70-87 years), who were active but non-exercising, a 10-wk RT intervention increased HDL-C and decreased TG compared to baseline values (228). Compared with the control group, the RT group had significantly lower LDL-C and TC after the intervention. Of note, body weight and diet were unchanged across groups.

A 2010 study by Lira et al. examined the effects of different acute RT loads on the lipid profile among healthy, untrained males (n=30) (231). Subjects were randomized into four intensity groups (50%-1 RM, 75%-1 RM, 90%-1 RM, and 110%-1 RM) and blood lipids were assessed at rest and after 1, 24, 48 and 72 h of RT. The total exercise volume was equalized between the groups to ensure that the RT intensity was the factor being assessed. The 75%-1 RM group had greater TG reduction vs. others; the 110%-1 RM group presented an increased TG concentration vs. the 50% and 75% groups. HDL-C was significantly elevated after RT in the 50%-1 RM and 75%-1 RM groups vs. the 110%-1 RM group. Accordingly, the 50%-1 RM group had greater HDL-C concentration than 110%-1 RM group after 48 h and 72 h, respectively. The 50% group showed lesser LDL-C concentration than 110% group after 24 h. It was concluded that the acute RT may induce changes in lipid profile in a specific-intensity manner, and low and moderate exercise intensities appear to be promoting more benefits on lipid profile than high intensity RT. The acute effects of RT sessions performed at different levels of high- (three sets with max of 15 repetitions) and low- (one set with max of 15 repetitions) volume RT on postprandial lipemia was investigated in postmenopausal women (232). One RT session involved eight exercises. At 16 h following RT, there were no significant differences in TC, LDL-C, HDL-C, and TG concentrations between the high-volume and the low-volume group.

A recent study by Vatani et al. examined the effects of a 6-wk moderate-intensity (45–55% 1 RM) and high-intensity (80-90% 1 RM) RT in healthy young men (n=30, 3 sessions/wk) (233). Both regimens significantly decreased TC, LDL-C and TC/HDL-C ratio, with no significant differences between groups, suggesting limited additional benefits of increasing the RT intensity. Interestingly, HDL-C concentration was found to be significantly increased only with the high-intensity regimen. Previous observations, however, have indicated that HDL-C is likely to be the first lipid profile response to PA and exercise, even at low intensities of activity (218).

In both elderly men and women (n=236, mean age: 74 years), Arnarson et al. studied the responses of blood lipids to a 12-wk RT (3 times/wk; 3 sets, 6-8 repetitions at 75-80% of the 1 RM) (234). The concentrations of TC, HDL-C, LDL-C, and TG decreased significantly. Reductions in fat mass as well as a gain in lean body mass were predictors of TG reductions, whereas the use of lipid-lowering drugs was a predictor of TC and LDL-C reductions.

COMBINED MODALITIES: AEROBIC EXERCISE AND RESISTANCE TRAINING

There is limited data on the effects of combined training modalities (CT) on blood lipid profile. Tambalis et al. reviewed the effectiveness of different types of exercise (AET, RT, and CT) in altering blood lipid levels (229). For CT protocols, the results were inconsistent: only three out of eight studies reported remarkable improvement in LDL-C (4% to 34% decrease) and HDL-C (3.5% to 23% increase), whereas TC and TG were significantly reduced only in two trials (229). Two other trials reported no significant alterations on the lipid profile in relation to the control group (216,235).

The effects of a 16-wk moderate-intensity CT protocol [AET at 60% HR_{max} with RT (two sets of 15 repetitions) at 60% 1 RM] was examined in previously untrained healthy young men (n = 28) (236). LDL-C reduced significantly following CT, without significant differences from those achieved by AET alone. It appears that no additional LDL-C reduction resulted from combining the two modes of exercise. Ha et al. combined 30 min of AET at 60-80% of the maximal heart rate reserve (maximal heart rate - heart rate at rest) [$HR_{reserve}$] with 30 min of RT at 12-15 repetitions maximum in 16 participants aged 20–26 years for 12 wks (237). The intervention significantly reduced the participants' waist circumference, body fat percentage and blood pressure values, compared with those of non-exercising controls. Reductions in TC, LDL-C and TG were observed in the exercising group but did not reach statistical significance when compared with values in the controls. The authors suggested that the participants were too young to elicit the clinical and significant effects shown by previous research in predominantly elderly or middle-aged participants.

A 2013 systematic review of 15 RCTs (≥8 wks duration, ~740 participants) compared the effects of different training modalities on anthropometric parameters, blood lipids, and cardiorespiratory fitness in overweight/obese subjects (BMI ≥25 kg/m^2, ≥19 years of age) (238). Compared to RT, AET resulted in a significantly more pronounced reduction of body weight, waist circumference, and fat mass. RT was more effective than AET in improving lean body mass. When comparing CT with RT, mean difference in change of body weight, waist circumference, and fat mass were all in favor of CT. There were no significant differences in blood lipid profile between modalities. It was concluded that the CT is the most efficacious means to reduce anthropometric outcomes and should be recommended in the prevention and treatment of overweight, and obesity whenever possible.

A 2014 comprehensive review by Mann et al. aimed to synthesizing the current published evidence regarding the impacts on cholesterol levels of AET, RT or both, based on 13 original research and two review articles (239). The authors confirm the beneficial effects of regular activity on cholesterol levels, and present evidence-based exercise recommendations aimed at facilitating the prescription and delivery of interventions for optimizing cholesterol levels. For patients with dyslipidemia, it is recommended to increase PA to >30 min/day for 5 times/wk; prolonged moderate-intensity AET at 70–80% $HR_{reserve}$, progressing to 85% HR_{max}, combined with moderate- to high-intensity RT at 75–85% 1 RM.

A 9-month community-based low-cost combined exercise program (aerobic, resistance, agility/balance, and flexibility exercise; three sessions/wk; 70 min/session) among middle-aged and older diabetic adults reduced TC by 7%, LDL-C by 11% and TG by 19%, and increased HDL-C by 7% (240).

LIPOPROTEIN (a)

Many population-based and cross-sectional studies have failed to detect an association between Lp(a) and PA level (241-248). However, in a large multicenter study of Finnish children

and young adults, PA was inversely correlated with Lp(a) concentration in a dose-dependent manner (249). Consistent with these findings, an inverse association between physical fitness and Lp(a) concentration was seen in young children and adolescents with diabetes mellitus (250). Furthermore, prolonged high-intensity exercise training may impact Lp(a) levels as experienced distance runners and body builders have been shown to have higher Lp(a) levels (251,252). However, intervention studies extending from a few weeks to four years have not reported any changes in median Lp(a) concentration in response to moderate exercise training, despite improvements in fitness and other plasma lipoprotein concentrations (245,253-256). Overall, the magnitude of exercise-induced changes in Lp(a) levels are modest and any impact related to specific apo(a) size isoforms has not been addressed.

Guidelines for Physical Activity and Exercise

AMERICAN HEART ASSOCIATION RECOMMENDATIONS FOR PHYSICAL ACTIVITY IN ADULTS

For overall cardiovascular health, the AHA guideline recommends at least 30 min of moderate-intensity aerobic activity at least 5 days/wk for a total of 150, or at least 25 min of vigorous aerobic activity at least 3 days/wk for a total of 75 min; or a combination of moderate- and vigorous-intensity aerobic activity, and moderate- to high-intensity muscle-strengthening activity at least 2 days/wk for additional health benefits. For lowering blood pressure and cholesterol it recommends an average 40 min of moderate- to vigorous-intensity aerobic activity 3 or 4 times/wk.

THE PHYSICAL ACTIVITY GUIDELINES FOR AMERICANS

The Physical Activity Guidelines for Americans (PAG) provides science-based guidance to help Americans (≥6 years old) improve their health through appropriate PA. The Office of Disease Prevention and Health Promotion (ODPHP), within the U.S. Department of Health and Human Services (HHS), led the development of the first ever PAG in 2008, and the subsequent PAG Midcourse Report in 2013. The PAG recommendations complement the Dietary Guidelines for Americans as well as other national health promotion and disease prevention efforts. For adults, the PAG recommends at least 150 min/wk of moderate-intensity, or 75 min/wk of vigorous-intensity aerobic PA, or an equivalent combination of moderate- and vigorous intensity aerobic activity. Aerobic activity should be performed in episodes of at least 10 minutes, and preferably spread throughout the week. For additional and more extensive health benefits, adults are recommended to increase their aerobic PA to 300 min/wk of moderate intensity, or 150 min/wk of vigorous intensity aerobic PA, or an equivalent combination of moderate- and vigorous-intensity activity. The guideline also notes of additional health benefits by engaging in PA beyond this amount, and recommends doing muscle-strengthening activities that are moderate or high intensity, involving all major muscle groups on ≥2 days/wk.

THE WORLD HEALTH ORGANIZATION GLOBAL RECOMMENDATIONS ON PHYSICAL ACTIVITY FOR HEALTH

WHO developed the "Global Recommendations on Physical Activity for Health" with the overall aim of providing national and regional level policy makers with guidance on the dose-response relationship between the frequency, duration, intensity, type and total amount of PA needed for the prevention of non-communicable diseases. PA includes leisure time PA (e.g., walking, dancing, gardening, hiking, swimming), transportation (e.g. walking or cycling), occupational (i.e. work), household chores, play, games, sports or planned exercise, in the context of daily, family, and community activities. For adults aged 18–64 years, it is recommended doing at least 150 min of moderate-intensity aerobic PA throughout the week, or doing at least 75 min of vigorous-intensity aerobic PA throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity. Aerobic activity should be performed in bouts of at least 10 minutes duration. For additional health benefits, the guideline recommends increasing moderate-intensity aerobic PA to 300 min/wk, or engaging in 150 min/wk of vigorous-intensity aerobic PA, or an equivalent combination of moderate- and vigorous-intensity activity. Muscle-strengthening activities involving major muscle groups are recommended on ≥2 days/wk.

Examples of current recommendations on PA and exercise are shown in Table 3.

Table 3. Examples of Recommendations on Physical Activity and Exercise

Guideline/Organization	Purpose	Type/Duration	Frequency	Total amount
The American Heart Association Recommendations for Physical Activity in Adults	Overall health	At least 30 min of moderate-intensity aerobic activity, or	5 days/wk	150 min
		At least 25 min of vigorous-intensity aerobic activity	3 days/wk	75 min
	Additional health benefit	Moderate- & vigorous-intensity aerobic activity with moderate to high-intensity muscle-strengthening activity	2 days/wk	-
	Lowering of cholesterol	An average 40 min of moderate- to vigorous-intensity aerobic activity	3 or 4 days/wk	120 min or 160 min

The Physical Activity Guidelines for Americans	Overall health (Adults)	At least 150 min/wk of moderate-intensity aerobic activity, or	At least 10 min episodes spread throughout the week	150 min
		75 min/wk of vigorous-intensity aerobic activity, or		75 min
		An equivalent combination of moderate- and vigorous-intensity aerobic activity		-
	Additional & more extensive health benefits	300 min/wk of moderate-intensity aerobic activity, or	Spread throughout the week	300 min
		150 min/wk of vigorous-intensity aerobic activity, or		150 min
		An equivalent combination of moderate- and vigorous-intensity activity		-
	Health benefits beyond above	Moderate- or high-intensity muscle-strengthening activities, involving all major muscle groups	At least 2 days/wk	
The World Health Organization Global Recommendations on Physical Activity for Health	Overall health benefits (Adults aged 18-64 years old)	At least 150 min of moderate-intensity aerobic activity, or	Bouts of at least 10 minutes duration	150 min
		At least 75 min of vigorous-intensity aerobic activity, or		75 min
		An equivalent combination of moderate- and vigorous-intensity activity		-
	Additional health benefits	300 min/wk moderate-intensity aerobic activity, or		300 min

	150 min/wk of vigorous-intensity aerobic activity, or		150 min
	An equivalent combination of moderate- & vigorous-intensity activity		-
	Muscle-strengthening activities, involving major muscle groups	At least 2 days/wk	-

Table 4. KEY POINTS: PHYSICAL ACTIVITY AND EXERCISE

1) PA impacts cardiovascular risk through beneficial effects on several factors, including blood lipids and lipoproteins.
2) A vigorous walk >150 min/week resulted in a 35% reduction of coronary events.
3) PA increases HDL-C level and lowers triglyceride level.
4) AET has variable effects on blood lipids with the most common change being an increase in HDL-C level (a mean increase of 4.6%).
5) A more intense AET may be needed to improve LDL-C or triglyceride levels.
6) AET volume, as opposed to intensity, maybe the key to improving the lipid profile.
7) Acute RT-induced changes in lipid profile maybe depend on intensity as regimens with a low or moderate intensity appeared to promote more benefits than high intensity RT.
8) Moderate and high intensity RT regimens decrease TC, LDL-C and TC/HDL-C ratio with no significant differences between groups, suggesting limited additional benefits of increasing RT intensity.
9) CT reduced LDL-C level but without significant differences from those achieved by AET alone.
10) There are no significant differences in blood lipid profile between CT and RT modalities.

Abbreviations: PA, physical activity; AET, aerobic exercise training; RT, resistance training; CT, combined modalities

FUNCTIONAL FOODS

Background

Functional food is a term that is used by different groups to describe food with potential health benefits. There is no universally accepted definition for a functional food. The International Food Information Council Foundation described functional foods as, “foods or food components that provide benefits beyond basic nutrition and may play a role in reducing or minimizing risk of certain diseases and other health conditions” (257,258). Oatmeal is an example of a functional food because it helps to lower cholesterol levels in addition to providing energy and nutrition.

Functional foods have been suggested to have the potential to reduce the risks associated with a number of diseases such as hyperlipidemia, CVD, diabetes, hypertension, bone disorders, immunological diseases, digestive disorders, and cancer (257,259,260). The use of functional foods has been increasing over the past two decades due to the increased interest in their potential health benefits (257).

Although there is no universally accepted definition of functional foods, several definitions have been proposed. The term functional food was first coined in Japan in the 1980's as FOSHU (Food for Specialized Health Uses) (261). FOSHU refers to "foods containing ingredients with functions for health and officially approved to claim its physiological effects on the human body", and is intended to be consumed for the maintenance or promotion of health or special health uses by people who wish to control health conditions, including blood pressure or blood cholesterol (261). In addition to the Japan Ministry of Health, Labor and Welfare, other organizations have offered definitions of functional food. The Academy of Nutrition and Dietetics defined functional foods as "whole foods along with fortified, enriched, or enhanced foods that have a potentially beneficial effect on health when consumed as part of a varied diet on a regular basis at effective levels" (259). The Academy of Nutrition and Dietetics stated “All foods are functional at some physiological level. Functional foods include whole foods and fortified, enriched, or enhanced foods that have a potentially beneficial effect on health when consumed as part of a varied diet on a regular basis, at effective levels” (262). Health Canada defines functional foods as being "similar in appearance to, or may be, a conventional food that is consumed as part of a usual diet, and is demonstrated to have physiological benefits and/or reduce the risk of chronic disease beyond basic nutritional functions" (263). The European Commission Concerted Action on Functional Food Science considers foods to be functional if they have a beneficial effect on one or more functions of the body and are still in the form of food, not a dietary supplement (264). No legal definition exists for functional foods in the United States, and there are no special regulations. FDA currently regulates functional foods under the Federal Food, Drug, and Cosmetic Act of 1938 and its amendments. Under these regulations, functional foods can be placed into a number of existing regulatory categories such as conventional foods, food additives, dietary supplements, medical foods or foods for special dietary use.

Beyond basic nutrients such as carbohydrates, proteins and fats, functional foods generally contain bio-active components that may provide health benefits. There are many potential bioactive components including dietary fiber, polyunsaturated fats (e.g. omega 3 fatty acids/ *n-3*), antioxidants, and plant sterols/stanols. The commonly accepted characteristics of functional foods are: 1) they are in a food form, 2) they provide health benefits beyond basic nutritional needs, and 3) they can be consumed as a part of the regular diet.

Dietary supplements are not considered functional foods as they are products in non-food form intended to supplement the diet. Functional foods could be classified based on 1) nature of origin, 2) degree of processing (whole foods, processed foods, conventional foods with enhanced bioactivity), and 3) health benefits. Functional foods based on their origin can be

classified into two groups: a) animal origin and b) plant origin. Widely used functional foods from animal origin are fish, fish products such fish oil, fortified eggs and milk products. Functional foods from plant origin include fruits, vegetables, nuts, seeds, fiber, whole grains, and spices. Functional foods based on processing could be categorized into three groups: a) whole foods, b) processed foods, and c) conventional foods with enhanced bioactivity. Whole foods are unprocessed and unrefined, or processed and refined as little as possible before being consumed. They naturally contain bioactive components and have not been fortified. Whole foods of plant origin include fruits and vegetables, nuts and seeds, beans and legumes, whole grains and fiber. Whole foods of animal origin include fish or dairy products. Processed functional foods do not generally contain natural bioactive components and these are added. Examples of processed functional foods include margarine spreads that contain *n-3* fatty acids, calcium-fortified orange juice, and folic acid enriched breads. Conventional foods with enhanced bioactivity are foods that naturally contain bioactive components but where the level has been modified or concentrated. Examples of conventional foods with enhanced bioactivity include yogurt with increased level of probiotics, tomatoes with increased levels of lycopene, and eggs with increased levels of *n-3* fatty acids.

Clinical research studies conducted on functional foods over the past two decades have indicated that some functional foods may be useful in preventing, reducing and or treating risks associated with lipid disorders, CVD, diabetes, obesity or hypertension (257,259,260,265). Several functional foods have lipid altering properties such as lowering TC, LDL-C, and/or TG and/or improving high HDL-C concentrations (Table 5). Below we focus on effects on lipid levels and discuss the efficacy of various functional foods in reducing TC, LDL-C, or TG levels and improving HDL-C levels and the supporting clinical evidence. In addition, we have examined the safety issues, and adverse effects of these functional foods.

Table 5. Potential Lipid Lowering Benefits of Functional Foods

Food	Food examples	Bio-active component	Potential health benefit
Fish	Fish, fish oil	*n-3* fatty acids	Reduces TG
Nuts & seeds	Almonds, walnuts etc.	Unsaturated fats, fiber, antioxidants & phytochemicals	Reduces TC and LDL-C
Fiber	Psyllium, pectin, wheat dextrin & oat fibers	Soluble fibers (viscous fibers) & insoluble fibers (non-viscous fibers)	Reduces TC and LDL-C
Vegetables & fruits	Apples, pear carrots, Brussel sprouts	Fiber, phytosterols & stanols	May help in lowering TC & LDL-C
Whole grain	Oats, barley, rye-based whole grain, red yeast rice & buckwheat	Fiber & bran	May help in lowering TC & LDL-C

Fortified/enriched functional foods	Margarines fortified with phytosterols, yogurt fortified with phytosterols	Phytosterols such as sitosterol, campesterol & stigmasterol	Reduces TC and LDL-C
Other foods	Wine	Phytosterols	May help to improve HDL-C

Fish and Fish Products

Clinical research studies conducted in the 1960s to early 2000s implicated differential effects of various types of fats on cardiovascular outcomes. These studies suggested that many saturated fatty acids (e.g. palmitic acid, mystric acid) and *trans* fatty acids could raise TC and/or LDL-C concentrations (65,266-270). In contrast, it was observed that there could be health benefits from the consumption of fish (e.g. oily fish) and fish products since it was found that Greenland Eskimos have a lower risk of heart disease despite consuming a high-fat diet (271,272). Several studies have suggested that these beneficial effects may be due to the presence of PUFAs (e.g. *n-3*, *n-6*) found in fish (273-276). The consumption of fish and fish products as part of the regular diet has been reported to reduce risk for a number of diseases/conditions such as CVD, blood clotting, arthritis, and vitamin and mineral deficiencies (277).

The market for fish and fish products has grown significantly in recent years because of the potential health benefits associated with fish consumption (278). Fish, especially salmon, mackerel, tuna, sturgeon, mullet, bluefish, anchovy, sardines, herring, trout, and menhaden are very rich sources of *n-3* fatty acids, and contain relatively lower amounts of saturated fats. The amount of *n-3* fatty acids and *n-6* fatty acids in fish can vary significantly depending on a number of factors such as the type of fish, location of the catch, fish diet, and season (279). While many have recommended the intake of fish with a larger ratio of *n-3* to *n-6* fatty acids, the long-term effects of intake of fish with greater *n-3* to *n-6* ratio is not fully understood. Fish such as salmon, mackerel, tuna, and herring can contain about 1,000 mg of *n-3* fatty acids in about 100 g of fish. Two main *n-3* fatty acids are found in fish and other sea products, eicosapentaenoic acid (EPA, 20:5) and docosahexaenoic acid (DHA, 22:6), believed to be responsible for the health benefits associated with fish oils. A summary of the EPA and DHA content of various fish is given in Table 6. EPA and DHA are mostly found in fish and other seafood, while another *n-3* fatty acid, alpha-linolenic acid (ALA, 18:3) is found mostly in nuts and seeds such as walnuts, flaxseed and some vegetable oils such as soybean and canola oils. The body is capable of converting ALA into EPA and DHA but the conversion rates are low and influenced by several factors such as smoking, environmental toxins, aging, excessive saturated fat intake, alcohol, and certain medications (280). *n-3* fatty acids, such as EPA and DHA, appear to reduce plasma TG by: a) reducing VLDL production by the liver, b) accelerating chylomicron and VLDL elimination from the blood, and c) converting fatty acids to energy (281). The preparation of fish has the potential to impact on health benefits, as many methods appear to

alter *n-3* fatty acid content. Baking and frying tend to result in breakup of the existing chemical bonds and frying can lead to the greatest losses in *n-3* fatty acid content.

Table 6. *n-3* Fatty Acid Content of Fish*

Fish Type	EPA (mg/100 g)	DHA (mg/100 g)	EPA+DHA (mg/100 g)
Anchovy European Canned	763	1,292	2,055
Salmon, Atlantic Farmed Cooked Dry Heat	690	1,457	2,147
Herring, Atlantic Cooked Dry Heat	909	1,105	2,014
Salmon, Atlantic Wild Cooked Dry Heat	411	1,429	1,840
Mackerel, Atlantic Cooked Dry Heat	504	699	1,203
Bluefish Cooked Dry Heat	323	665	988
Sardines, Atlantic	473	509	982
Trout Mixed Species Cooked Dry Heat	259	677	936
Tilefish Cooked Dry Heat	172	733	905
Swordfish Cooked Dry Heat	138	681	819
Tuna White Canned	233	629	862
Shark Mixed	316	527	843
King Mackerel Cooked Dry Heat	174	227	401

* Adapted from US Department of Agriculture (USDA) Reference: (282)

POTENTIAL HEALTH BENEFITS

Consumption of fish and fish products has been initially reported to provide several health benefits, including lowering of TG, reducing the risk of CVD, modest lowering of blood pressure, and lowering the risk of stroke (283,284). Reports of a TG lowering effect from *n-3* fatty acids from fish and fish oil go back more than 50 years (284,285). Subsequently several studies (observational, interventional and meta-analysis) were undertaken to ascertain these findings (286-291). The major findings of these studies are: a) reduction of TG levels was observed with fish and fish oil intake in several studies (286-292), b) both DHA and EPA can reduce TG, c) a

higher TG reduction (25-30%) was observed with high doses (4 g/day) of EPA+DHA (287,289,290,292-294), d) a greater reduction in TG levels was observed in individuals with a higher baseline TG level (290,295), e) TG lowering effects of fish oil are not significant with low doses of EPA+DHA more typical of Western diets (295), and f) a dose dependent relationship was observed between the consumption of *n-3* fatty acids and the TG lowering effect (289,290). In other studies, supplementation with omega-3 carboxylic acids lowered TG and apoCIII (296,297). In addition, it was reported that eicosapentaenoic acid ethyl ester can not only lower TG but also remnant-like particle cholesterol in the MARINE and ANCHOR studies (298). A recent meta-analysis of 47 studies demonstrated that an average daily intake of 3.25 g of EPA and/or DHA reduced TG by 0.34 mmol/L (30 mg/dL) in hyperlipidemic subjects (299). In another meta-analysis of 38 studies, a reduction in TG levels was noted with ≥4 g/day of n-3 PUFA from either marine or EPA/DHA-enriched food sources (9-26% reduction in TG) or with 1-5 g/day of EPA and/or DHA from supplements (4-51% reduction in TG) (300).

The findings on the effects of fish oil on TC and LDL-C are more mixed (289,290). While PUFAs may lower LDL-C in some studies, this has not been found in studies with fish-based products. Some authors report a slight increase in LDL-C while other studies did not show any significant changes in LDL-C (289,290). DHA and EPA may have differential effects on LDL-C with DHA slightly increasing LDL-C and EPA slightly decreasing LDL-C (286,291). In dyslipidemic and diabetic patients, apoB-100 and LDL-C levels showed a divergent pattern, with no change or a slight decrease in apoB-100 levels and a significant increase in LDL-C (289). Fish oil appears to have influences on LDL particle size, particularly the number of small, dense LDL particles (294,301-303), likely associated with reductions in TG. Eicosapentaenoic acid ethyl ester can not only lower TG but also lower total and small LDL particles (304).

In contrast to the effect on TG, the influence of fish oil on HDL-C has also been inconsistent. In mouse studies, HDL-C increased after consumption of fish oil compared to sunflower oil for 16 weeks (305). In some human studies, only a small increase in HDL-C as a result of *n-3* fatty acid intake has been noted (289,290). Of note, the meta-analysis by Eslick did not show an effect on HDL-C (299). This meta-analysis also did not show an effect on LDL-C. There are two fish oil supplements (e.g. Lovaza) that have been approved by the FDA to lower TG.

A large body of experimental, clinical, and epidemiologic research has explored potential benefits of EPA- and DHA-rich fish oil on cardiovascular health (283,289,290,306,307). Findings from prospective observational cohort investigations indicate that regular consumption of fatty fish (twice/wk) is associated with a significantly lower risk of cardiovascular death (307,308). Several randomized clinical trials have examined the effects of fish oil supplementation on nonfatal myocardial infarction, ischemic stroke, atrial fibrillation, recurrent ventricular arrhythmias, and heart failure, but results have been inconsistent (307,308). In the Norfolk-based European Prospective Investigation into Cancer cohort, the use of omega-3 polyunsaturated fatty acid (*n-3* PUFA) supplements (utilized mainly cod liver oil) was associated with a lower hazard of CHD mortality in a population with low fish consumption over a 19 year period (309). Two earlier open-label trials, the Prevenzione trial (310) and the Japan EPA Lipid

Intervention Study (311), found significant benefits of fish oil supplementation on CVD outcomes. The AHA has provided a recommendation to consider use of fish oil supplementation in subjects with a recent myocardial infarction or heart attack (312).

There is uncertainty regarding the benefit from use of omega-3 supplementation in established CVD. The recent ALPHA OMEGA (313), OMEGA (314), and SU.FOL.OM3 (315) clinical trials did not find such benefits. To date, there is no conclusive evidence to recommend fish oil supplementation for primary or secondary prevention of CVD (316). A meta-analysis of 10 trials involving 77,917 individuals reported that omega-3 fatty acid supplementation had no significant association with coronary heart disease death, nonfatal myocardial infarction, nonfatal coronary heart disease or any major vascular events (317).

SAFETY CONCERNS

When taken in low doses (≤3 g/day), intake of fish oil is likely to be safe for most people, including pregnant and breast-feeding women (318). There are some safety concerns when fish oil is consumed in high doses as an intake of more than 3 g per day might impact blood clotting and increase the chance of bleeding (318). Other side effects from intake of fish oil can include bad breath, heartburn, nausea, loose stools, rash, and nosebleeds. Using fish oil together with antihypertensive drugs may result in a small but statistically significant reduction in blood pressure (319-325). *n-3* fatty acids may affect the heart rate for subjects with a heart transplant, and high doses of fish oil might impact the immune system. While some fish such as swordfish, king mackerel, tilefish, and albacore tuna may carry a higher risk of mercury poisoning, fish oil has not been found to carry a significant risk.

DIETARY GUIDELINES

The AHA recommends consumption of two servings of fatty fish per week (e.g. salmon, mackerel, trout, sardines and tuna) (13). This is because these fish are high in EPA and DHA. These *n-3* fatty acids, EPA and DHA, have been accepted by the AHA and Endocrine Society to help lower TG (326,327). FDA has authorized a qualified health claim on dietary supplements linking the consumption of EPA and DHA (*n-3*) fatty acids to a reduction of CHD risk. U.S. health organizations recommend a daily EPA+DHA intake of 250 mg for most people and 1,000 mg for those with CVD. Higher dosages of *n-3* fatty acids are required to reduce elevated TG levels (2-4 g per day) and to reduce morning stiffness and joint pain in patients with rheumatoid arthritis (at least 3 g per day). Modest decreases in blood pressure occur with significantly higher dosages of *n-3* fatty acids. The 2010 Dietary Guidelines for Americans recommend consuming at least 8 ounces of seafood per week to reach an average daily intake of 250 mg per day for a total of 1,750 mg of EPA and DHA per week (328).

Nuts and Seeds

Nuts and seeds are functional foods of plant origin. The energy content of nuts and seeds is mainly derived from fat and protein, while the carbohydrate content is less compared to beans and legumes. Consumption of nuts in moderate amounts has been found to provide health benefits such as reducing cholesterol levels (329-331) and lowering CHD risk (331-333). Limited evidence also exists for beneficial effects on hypertension, cancer, and inflammation. The most consumed edible tree nuts are almonds, hazelnuts, walnuts, pistachios, pine nuts, cashews, pecans, macadamias and Brazil nuts. Peanuts are botanically groundnuts or legumes, and are widely considered to be part of the nuts food group. Nuts are generally consumed as snacks (fresh or roasted), in spreads (peanut butter, almond paste), or as oils or baked goods. Seeds come in all different sizes, shapes and colors. Popular seeds include flax seeds, pumpkin seeds, sunflower seeds, chia seeds, sesame seeds and mustard seeds.

Nuts and seeds are rich in MUFAs, such as oleic acid and in PUFAs, such as linoleic acid and (ALA). They also contain small amounts of saturated fat. Almonds, cashews, hazelnuts, pistachios and macadamian nuts have a high MUFA content (>50%) content when compared with other nuts. For other nuts (e.g. Brazil nuts, pine nuts, and walnuts) the PUFA content is high (>50%), while peanuts and pecans have been found to contain relatively high levels of both MUFA and PUFA (Table 7). Nuts are a good source of dietary fiber, ranging from 4-11 g/100 g. Phytochemicals present in nuts include carotenoids, phenols and phytosterols. In all nuts, “most of the antioxidants are located in the pellicle or outer soft shell” (331). The beneficial effects of nuts and seeds are likely due to the presence of unsaturated fats, fiber, antioxidants, and phytochemicals (334,335). The fatty acid profile and fat content of nuts is suggested to be responsible for observed health benefits, particularly the lipid altering effects, associated with the consumption of nuts and seeds (334). Antioxidants and phytochemicals present in nuts and seeds may also contribute to cardioprotective properties and cholesterol lowering (335). The individual contribution of each of these bioactive components is not yet fully known, and further studies are needed to understand their mechanism of action.

Table 7. Nutrient Composition of Nuts*

Nuts	PUFA (g/100 g)	MUFA (g/100 g)	SFA (g/100 g)	Fiber (g/100 g)
Walnuts	47.2	8.9	6.1	6.7
Peanuts	15.6	24.4	6.3	8.8
Pistachios	13.7	23.8	5.6	10.3
Almonds	12.3	31.6	3.8	12.5
Hazelnuts	7.9	45.7	4.5	9.7
Cashews	7.8	23.8	7.8	3.3
Pecans	21.6	40.8	6.2	9.6
Macadamias	1.5	58.9	12.1	8.6

* Data from US Department of Agriculture, Agricultural Research Service (336).

POTENTIAL HEALTH BENEFITS

In the past 25 years, a number of studies have been carried out on the potential health effects of nuts and seeds, including feeding trials to investigate the effect of nut consumption on blood lipids and other biological indexes of heart disease (329-333,337-339). Walnuts and almonds are among the most studied nuts. Fewer studies have been conducted on peanuts, pecans, macadamia nuts, hazelnuts, and pistachios. To date, there is even less experience with Brazil nuts, cashews, or pine nuts. Health benefits of seeds, including flax seeds and chia seeds have generally attracted fewer studies. Consumption of nuts and seeds may be effective for lowering TC and LDL-C and for improving the LDL-C/HDL-C ratio in healthy subjects or patients with moderate hypercholesterolemia (331-333,337-340). Nuts had no significant or minimal effect on reducing TG or increasing HDL-C. It was also noted that consumption of nuts and seeds was beneficial in reducing CVD (332,338). Health benefits of nuts and seeds vary significantly depending on the type and nutrient composition and quantity consumed.

There are several trials that show reductions in cholesterol and TG with the consumption of walnuts. The Loma Linda University walnut study, a 4-wk trial where the consumption corresponded to 20% of the daily caloric intake, was one of the first to investigate effects of a diet rich in walnuts on cholesterol levels (330). Some of the major findings included a decrease in TC and LDL-C (by 12% and 16-18%, respectively), and a decrease in the LDL-C/HDL-C ratio of 12% (330,332,338). In another trial, the isocaloric replacement of macronutrients (either reduction of carbohydrates, fat, or both) with walnuts (43 g/day) resulted in reductions in fasting TC, non-HDL-C, LDL-C, TG and apo B (walnut vs. control: TC −8.5 ± 37.2 mg/dL; non-HDL-C −10.3 ± 35.5 mg/dL, LDL-C −7.4 ± 32.4 mg/dL, TG −5.0 ± 47.5 mg/dL and apoB −6.7 ± 22.4 mg/dL) (341). Several subsequent studies have confirmed the effects of walnut consumption (~40 to 85 g/day) to lower LDL-C (342-344). In another trial, the effect of walnut oil consumption on lipid profiles in individuals with T2DM was examined and it also showed a reduction of TC -30.04 mg/dL, LDL-C -30.44 mg/dL, and TG -15.04 mg/dL (345). A meta-analysis on the effect of walnuts on lipid levels that included 365 participants showed a decrease in TC and LDL-C (10.3 mg/dL and 9.2 mg/dL, respectively), while HDL-C or TG were not significantly affected (344). In another meta-analysis that analyzed 1,059 participants with walnut enriched diets, blood lipids were lowered: TC by -6.99 mg/dL, LDL-C -5.51 mg/dL and TG -4.69 mg/dL. This study reported greater reductions of TC = -12.30 mg/dL, LDL-C = -8.28 mg/dL, apoB -3.74 mg/dL when compared with Western diets reductions (346). Some have suggested that walnut consumption may alter the composition and function of the human gastrointestinal microbiota, including firmicutes species (e.g. butyrate-producing Clostridium species, Faecalibacterium and Roseburia) (347). This may contribute to alterations in urolithins and secondary bile acids that could contribute to alterations in cholesterol sub fractions (347,348).

Cholesterol-lowering effects have also been observed with consumption of almonds, hazel nuts, pistachios, and peanuts. In studies on almonds (50-100 g/day), TC and LDL-C decreased by 4-16% and 7-19%, respectively (329,349). There was minimal lowering in TC and LDL-C at an

almond intake of 50 g/day (corresponding to approximately a half cup of almonds). In one trial, overweight individuals with an intake of ~45 g of almonds had a decrease in non-HDL-C (-6.9 ± 2.4 mg/dL) and LDL-C (-5.3 ± 1.9 mg/dL) (350). However, the intake of 100 g/day did not result in statistically significant LDL-C and non HDL-C changes in obese individuals in another trial (351). While intake of ~43 g of almonds resulted in an increase in HDL-C in normal weight subjects, this effect was not seen in the overweight or obese group (352). Interventional studies with hazelnuts (353), pistachios (354), and peanuts (355) showed LDL-C reductions ranging from 4% to 11%. A meta-analysis of three studies, hazelnuts intake (30 g to 60 g/day) resulted in a reduction of LDL-C by ~5.8 mg/dL (356). In a review which analyzed 9 trials that added pistachios to the diet, it was reported that LDL-C/HDL-C ratio decreased with supplementation (357). In one trial that required subjects to consume pistachios daily (57 g/day ~ 3/8 cup), the non-HDL particles decreased compared with controls (358).

Subjects who intake a mixture of nuts appear to have reductions in LDL-C in many studies. A pooled analysis examining the effects of various nuts on TC and LDL-C levels reported a reduction in TC and LDL-C (5% and 7%, respectively) with an average daily intake of 67 g of nuts (332). A trial with mixed almonds and/or hazelnuts (~30 g/day) resulted in ~5.8 mg/dL reduction in LDL-C (359). As in other studies, it was also noted that the cholesterol lowering effect was dose dependent, and that dose-related effects were observed in both men and women. In addition, an inverse association between cholesterol responses and BMI was seen during consumption of large quantities of nuts. A Mediterranean diet supplemented with 30 g of mixed nuts/day (15 g walnuts, 7.5 g hazelnuts, and 7.5 g almonds) showed beneficial effects on the lipid profile in the PREDIMED study (360). The addition of nuts to a Mediterranean diet may render the LDL-C particles to be less atherogenic (361). Other studies have noted that the estimated cholesterol lowering effect of nuts was greater in individuals with higher initial values of LDL-C and in those with a lower baseline BMI (331). However, not all studies noted reductions in LDL-C with intake of a nut mixture. In one Chinese study, nut consumption was not associated with significant LDL-C reductions (362).

The effect of flaxseed has also been investigated. Pan et al. conducted a meta-analysis to examine the effectiveness of flaxseed and its derivatives on blood lipid profiles (363). Some of the major findings of this study were that whole flaxseed reduced TC and LDL-C by 0.21 and 0.16 mmol/L (6 and 8 mg/dL), respectively. This study noted that lignin supplements reduced TC and LDL-C by 0.28 mmol/L and 0.16 mmol/L (11 and 8 mg/dL) respectively while there was no significant reduction of TC or LDL-C levels observed with flaxseed oil (363). In a study with milled flaxseed, LDL-C reduction was seen in patients with PAD, who were on cholesterol lowering medications, by about 0.4 mmol/L (~15.4 mg/dL) after 6 months of flaxseed use (364). While intake of flaxseed may alter LDL-C, it does not appear to significantly shift the fecal metabolome (365). The cholesterol-lowering effects were more apparent in individuals with elevated baseline cholesterol concentrations. The functional food intervention did not result in significant changes in HDL-C or TG levels.

SAFETY CONCERNS

There are two major concerns associated with nut consumption, a possible weight gain (329,366) and allergic reactions (367). There is considerable evidence indicating that there are no adverse effects of nut consumption in moderate quantities on energy balance or body weight (65,85). However, nuts can cause allergies in some individuals with an estimated prevalence rate of approximately 1% in the general population (367). Allergic reactions to nuts are due to allergenic seed storage proteins that elicit specific IgE antibodies. An additional concern is potential toxicity through contamination of nuts with mycotoxins, particularly aflatoxins. Flaxseed is likely safe for most adults although adding flaxseed to the diet might increase the number of bowel movements and might also cause gastrointestinal side effects such as bloating, gas, abdominal pain, constipation, diarrhea and nausea. Higher doses are likely to cause more such side effects.

DIETARY GUIDELINES

The 2010 Dietary Guidelines for Americans state that nuts and seeds can be a good source of protein and monounsaturated and polyunsaturated fats (328). The 2010 Dietary Guidelines for Americans recognizes that eating some type of nuts (e.g. peanuts, walnuts, almonds, and pistachios) may reduce risk factors for CVD and recommend consuming unsalted nuts and seeds (328). According to the FDA, the cardiovascular risk factor reduction is limited to “almonds, hazelnuts, peanuts, pecans, some pine nuts, pistachio nuts, and walnuts… that do not exceed 4 g saturated fat per 50 g of nuts” (368). The AHA recommends eating four servings (“a small handful, 1.5 ounces, of whole nuts or 2 tablespoons of nut butter”) of unsalted nuts a week. Raw or dry-roasted nuts rather than those cooked in oil are recommended.

Fiber

Fiber is defined as the edible carbohydrate portion of plants resistant to enzymatic digestion (e.g. hydrolysis) and absorption in the human intestine. Fiber contains various chemical compounds or biopolymers that are water soluble/more fermentable (e.g., pectins, β-glucans, oligosaccharides, resistant dextrins, inulin, guar gum, other gums, fructans) and water insoluble/less fermentable (cellulose, hemicelluloses such as arabinoxylans, lignin, waxes, chitins, resistant starch) (369-374). Fiber is found mostly in fruits, vegetables, whole grains, nuts, seeds, psyllium seeds, beans and legumes. Fiber is known for its ability to provide bulk to stool and prevent or relieve constipation. In addition, fiber provides several other significant health benefits including lowering blood cholesterol concentrations by interfering with cholesterol absorption and reabsorption of bile acids (375,376). Fiber from beans, oats, flaxseed or oat bran are reported to lower TC and LDL-C levels (377). They may also slow the absorption of sugar and help improve blood glucose levels (375,378,379), aid in weight loss (380), and reduce obesity (381).

Fibers are generally classified into two types: soluble fibers (viscous fibers) and insoluble fibers (non-viscous fibers). Soluble fibers (e.g. hemicelluloses, pectins, guar gum, resistant starch,

inulin, oligosaccharides) dissolve in water and are readily fermented to short-chain fatty acids in the large intestine. They are present in all types of peas and beans like lentils, split peas, guar beans, pinto beans, black beans, kidney beans, garbanzo beans and lima beans, as well as in oats, barley, and some fruits and vegetables like apples, oranges and carrots. Fiber from psyllium seed, an ingredient in some over-the-counter laxatives, is also part of this group. Soluble fibers are generally effective in lowering TC and LDL-C levels. Insoluble fibers contain substances/chemicals such as cellulose, hemicellulose and lignin and are present in foods such as whole-wheat flour, wheat bran, nuts, beans and vegetables (e.g. cauliflower, green beans). The skins of fruits and vegetables are good sources of insoluble fiber. Wheat dextrin (wheat bran) is another good source of insoluble fiber, and is added to many dry breakfast cereals. Most foods contain both types of fibers. Insoluble fibers have a laxative effect but have a lower hypolipidemic response compared with soluble fibers. A summary of the fiber content of some foods is given in Tables 8.

Table 8. Fiber Content of Selected Vegetables*

Vegetables	Serving Size	Total Fiber/ Serving (g)	Soluble Fiber/ Serving (g)	Insoluble Fiber/ Serving (g)
Cooked vegetables				
Turnip	½ cup	4.8	1.7	3.1
Peas, green, frozen	½ cup	4.3	1.3	3.0
Okra, frozen	½ cup	4.1	1.0	3.1
Potato, sweet, flesh	½ cup	4.0	1.8	2.2
Brussels sprouts	½ cup	3.8	2.0	1.8
Asparagus	½ cup	2.8	1.7	1.1
Kale	½ cup	2.5	0.7	1.8
Broccoli	½ cup	2.4	1.2	1.2
Carrots, sliced	½ cup	2.0	1.1	0.9
Green beans, canned	½ cup	2.0	0.5	1.5
Beets, flesh only	½ cup	1.8	0.8	1.0
Tomato sauce	½ cup	1.7	0.8	0.9
Corn, whole, canned	½ cup	1.6	0.2	1.4
Spinach	½ cup	1.6	0.5	1.1
Cauliflower	½ cup	1.0	0.4	0.6
Turnip	½ cup	4.8	1.7	3.1
Raw vegetables				
Carrots, fresh	1, 7 ½ in. long	2.3	1.1	1.2
Celery, fresh	1 cup chopped	1.7	0.7	1.0

Onion, fresh	½ cup chopped	1.7	0.9	0.8
Pepper, green, fresh	1 cup chopped	1.7	0.7	1.0
Cabbage, red	1 cup	1.5	0.6	0.9
Tomato, fresh	1 medium	1.0	0.1	0.9
Mushrooms, fresh	1 cup pieces	0.8	0.1	0.7
Cucumber, fresh	1 cup	0.5	0.2	0.3
Lettuce, iceberg	1 cup	0.5	0.1	0.4

* Adapted from Anderson JW. *Plant Fiber in Foods*. 2nd ed. HCF Nutrition Research Foundation Inc, PO Box 22124, Lexington, KY 40522, 1990.

Table 9. Fiber Content of Selected Legumes*

Legumes (cooked)	Serving Size	Total Fiber/ Serving (g)	Soluble Fiber/ Serving (g)	Insoluble Fiber/ Serving (g)
Kidney beans, light red	½ cup	7.9	2	5.9
Navy beans	½ cup	6.5	2.2	4.3
Black beans	½ cup	6.1	2.4	3.7
Pinto beans	½ cup	6.1	1.4	4.7
Lentils	½ cup	5.2	0.6	4.6
Black-eyed peas	½ cup	4.7	0.5	4.2
Chick peas, dried	½ cup	4.3	1.3	3
Lima beans	½ cup	4.3	1.1	3.2

* Adapted from Anderson JW. *Plant Fiber in Foods*. 2nd ed. HCF Nutrition Research Foundation Inc, PO Box 22124, Lexington, KY 40522, 1990.

Table 10. Fiber Content of Selected Fruits*

Fruits	Serving Size	Total Fiber/ Serving (g)	Soluble Fiber/ Serving (g)	Insoluble Fiber/ Serving (g)
Apricots, fresh w/skin	4	3.5	1.8	1.7
Raspberries, fresh	1 cup	3.3	0.9	2.4
Figs, dried	1 ½	3	1.4	1.6
Mango, fresh	½ small	2.9	1.7	1.2
Orange, fresh	1 small	2.9	1.8	1.1
Pear, fresh, w/skin	½ large	2.9	1.1	1.8
Apple, red, fresh w/skin	1 small	2.8	1	1.8

Strawberries, fresh	1 ¼ cup	2.8	1.1	1.7
Plum, red, fresh	2 medium	2.4	1.1	1.3
Applesauce, canned	½ cup	2	0.7	1.3
Apricots, dried	7 halves	2	1.1	0.9
Peach, fresh, w/skin	1 medium	2	1	1
Kiwifruit, fresh	1 large	1.7	0.7	1
Prunes, dried	3 medium	1.7	1	0.7
Grapefruit, fresh	½ medium	1.6	1.1	0.5
Blueberries, fresh	¾ cup	1.4	0.3	1.1
Cherries, black, fresh	12 large	1.3	0.6	0.7
Banana, fresh	½ small	1.1	0.3	0.8
Melon, cantaloupe	1 cup cubed	1.1	0.3	0.8
Watermelon	1 ¼ cup cubed	0.6	0.4	0.2
Grapes, fresh w/skin	15 small	0.5	0.2	0.3
Raisins, dried	2 tbsp	0.4	0.2	0.2

* Adapted from Anderson JW. *Plant Fiber in Foods*. 2nd ed. HCF Nutrition Research Foundation Inc, PO Box 22124, Lexington, KY 40522, 1990.

Table 11. Plant Sterol and Stanol Contents in Different Foods*

Food item	***Plant Sterols (mg/100 g)***	***Plant Stanols (mg/100 g)***
Vegetable oils		
Corn oil	686-952	23-33
Rapeseed oil (canola oil)	250-767	2-12
Soybean oil	221-328	7
Sunflower oil	263-376	4
Olive oil	144-193	0.3-4
Palm oil	60-78	Traces
Cereals		
Corn	66-178	-
Rye	71-113	12-22
Wheat	45-83	17
Barley	80	2
Millet	77	-

Rice	72	3
Oats	35-61	1
Vegetables		
Broccoli	39	2
Cauliflower	18-40	Traces
Carrot	12-16	Traces
Lettuce	9-17	0.5
Potato	7	0.6
Tomato	7	1
Fruits and berries		
Avocado	75	0.5
Passion fruit	44	Not detected
Raspberry	27	0.2
Orange	24	Not detected
Apple	12-18	0.8
Banana	12-16	Not detected

* Adapted from Piironen V and Lampi AM (2004) (382)

The mechanism of action of fibers is not fully understood. Initially, the observed cholesterol-lowering benefits were ascribed to solubility effects and binding of bile acids with subsequent fecal elimination (383), requiring an enhanced formation of bile acids from cholesterol. Soluble fibers slow the digestive process which could result in a slow uptake of sugars. Recent studies have indicated that other fiber properties such as formation of gels and extent of fermentation ability might also contribute to the observed physiological effects of the fibers (384). The formation of gels slows gastric emptying, and contributes to levels of satiety. Soluble fiber and resistant starch molecules can be fermented by bacteria in the large intestine to produce short chain fatty acids, which may impact circulating cholesterol levels and hepatic cholesterol synthesis (385).

POTENTIAL HEALTH BENEFITS

Potential health benefits of fibers include a tendency to lower cholesterol and blood glucose levels (377), contributing to weight loss and obesity reduction, as well as lowering blood pressure (386). These actions may translate to reducing the risk of development or slow the progress of several diseases such as CVD (387), diabetes (378), stroke (388), hypertension (386,389) and gastrointestinal disorders (390). Public awareness of the health benefits of dietary fibers has increased over the past two decades; supermarkets now generally list the content of dietary fiber in most food labels.

The intake of fiber lowered TC and LDL-C levels. Several meta-analyses show that an average intake of 7-10 g/day of fiber (e.g. pectin and psyllium) can lower TC and LDL-C levels by ~0.13 mmol/L (5.1mg/dl) (391). A meta-analysis of 26 RCTS with diets rich in fiber (e.g. high content of pulses, pectin, gum, and psyllium) noted that there were reductions of LDL-C (~0.17 mmol/L) (6.6mg/dl) (392). A meta-analysis of 23 RCTs that used a variety of fiber sources, reported there were reductions in TC (~-0.23 mmol/L) (9.0mg/dl) and LDL-C (-0.14 mmol/L) (5.5mg/dl) with increased fiber intake (393).

The extent of LDL-C lowering depends on the fiber type, quantity and frequency of consumption. Intake of soluble fiber at a level of 5-15 g/day has been shown to reduce LDL-C concentrations by 5–13% in both men and women (375,394,395). A mean reduction in LDL-C concentrations of 0.029 mmol/L (or about 1 mg/dL) can be expected for each g of water-soluble fiber in the diet (377). A meta-analysis, including 67 controlled trials was conducted to determine the cholesterol-lowering effects of dietary fibers (377). The major findings were that consumption of soluble fibers (e.g. psyllium, pectin, wheat dextrin and oat products) were observed to reduce TC and LDL-C levels in many studies. A meta-analysis of 14 RCTs on the effect of barley β-glucan (e.g. 6.5 to 6.9 g/day) resulted in LDL-C reduction (~-0.25 mmol/L) (9.8mg/dl) and non-HDL-C (~-0.31 mmol/L) (12.1mg/dl) (396). The consumption of 3 g of barley β-glucan appears to decrease TC and increase bile acid synthesis without significantly affecting cholesterol absorption and synthesis (397). A RCT using α-cyclodextrin (α-CD), a soluble dietary fiber, resulted in a reduction of small-LDL particle number (~10%) (398). In another trial, α-cyclodextrin (α-CD) lowered acute PP blood TG levels (399).

Greater TC and LDL-C reductions were found with increasing fiber intake and a 10-15% reduction of TC and LDL-C observed with a high fiber consumption (10-30 g/day). Individuals who adhered to higher fiber content based Swedish nutrition recommendations in the Malmö Diet and Cancer cohort had lower LDL-C and TG (400). In the TOSCA.IT Study, an intake of ≥15 g fiber/1000 kcal was associated with an improved plasma lipids profile (401). While there were significant differences between genders for change in TC and LDL-C in the TOSCA.IT Study, it was not clearly explained by fiber intake (402). However, minimal reductions in LDL-C were observed with fiber intakes of 3 g/day. Furthermore, the efficacy of soluble fibers from oat, psyllium or pectin was not significantly different. The meta-analysis also reported a minimal to moderate reduction in HDL-C, but not in TG levels. Studies have indicated that CHD prevalence was significantly lower (29%) in individuals with the highest intake of dietary fiber compared to those with the lowest intake (375,394,395).

The fiber intake may not fully negate the type of fat intake and diabetes. A higher fat and meat intake despite similar fiber intake in western diets vs. traditional Japanese diet was associated increased TC and LDL-C (403). In one trial, the consumption of starch-restricted, fiber-rich functional bread (7 g) with a beta glucan/starch ratio of (7.6:100, g/g) did not alter TC of LDL-C in people with T2DM (404). In a cross-sectional survey of individuals with T2DM, a diet high in dietary fiber was associated with lower TG (405).

SAFETY CONCERNS

Some insoluble fibers have an affinity to bind minerals, including calcium, magnesium, phosphorous and iron. An excess fiber intake may cause abdominal discomfort, gas, and diarrhea.

DIETARY GUIDELINES

The 2010 Dietary Guidelines for Americans notes that good sources of fiber include vegetables, fruits, whole grains, bran, navy beans, lentils, pinto beans, black beans and split peas (328). It is important to note the sources of fiber because most Americans have a dietary intake of about < 15 g of fiber per day (328). The 2010 Dietary Guidelines for Americans note that foods high in fiber can not only promote a sense of fullness and laxation, but also may help reduce the risk of CVD (328). Guidelines from the Institute of Medicine/National Academy of Sciences are based on epidemiologic studies of fiber intake. The 2005 dietary reference intake guideline table from the Institute of Medicine has recommendations of dietary fiber for specific age groups, at estimated mean energy intakes: 1-3 years, 19 g/day; 4-8 years, 25 g/day; 9-13-year-old boys, 31 g/day; 9-13-year-old girls, 26 g/day; 14-18-year-old boys, 38 g/day; and 14-18-year-old girls, 26 g/day. The 2010 Dietary Guidelines for Americans recommend a fiber intake of about 25 g for teenage girls and women within the age range of 31-50 years (328). Teenage boys and men under 50 years of age are recommended a daily intake of 31-34 g of dietary fiber (328).

Fruits and Vegetables

Vegetables and fruits are considered functional foods and contain macronutrients (healthy fats, carbohydrates), micronutrients (vitamins and minerals), soluble fibers (β-glucans, psyllium, pectin), insoluble fibers and phytochemicals with potentially protective or disease preventive properties. A diet rich in vegetables and fruits is recommended to maintain health (406-409). Fruits and vegetables have less calories/unit weight compared to animal-based foods and do not contribute substantially to overall energy consumption. Botanists define fruit as a part of the plant that develops from a flower and contains seeds. Avocado, beans, and tomatoes are technically fruits. A vegetable is a part of plant that is edible and includes the stems, leaves, flowers, and roots. Examples include celery (stem), lettuce (leaves), cauliflower and broccoli (buds), and beets, carrots and potatoes (roots). Vegetables are in general less sweet or tart than fruits. Health benefits of fruits and vegetables are considered to be due to the presence of bioactive components such as fiber, healthy fats, and phytochemicals (410,411).

Fiber is present in many vegetables, fruits (Tables 8 and 10). Soluble fibers are present in all types of peas and beans (Table 9) and in some fruits and vegetables. Fiber-rich fruits include apples, pears, berries (e.g. strawberries) and citrus (orange, lemons). Many fruits and vegetables contain phytochemicals (Table 11), also known as plant chemicals, and more than 5,000 phytochemicals have been identified. Phytochemicals have antioxidant properties and have been suggested to reduce the risk of developing several diseases such as cancer, CVD,

neurodegenerative diseases and immunological disorders. Phytochemicals can be classified into broad categories such as phenolics, carotenoids, alkaloids, organonitrogen compounds, organosulfur compounds, and phytosterols.

Phenolics, compounds containing aromatic rings with one or more hydroxyl groups, are abundant compounds found in vegetables and fruits. Phenolics include phenolic acids, flavonoids, stilbenes, coumarins, and tannins (412-414). Phenolic acids account for approximately 1/3 of the phenolics in our diet and the remaining 2/3 originate from flavonoids (412). Wild blueberry and blackberry have the highest total phenolic content, followed by pomegranate, cranberry, blueberry, plum, raspberry, strawberry, red grape, and apple. Some of the best studied polyphenol-rich foods are tea, blueberries, extra-virgin olive oil, red wine, citrus fruits, hibiscus tea, dark chocolate, coffee, turmeric and other herbs and spices. Apples contribute approximately a third of fruit phenolics consumed by Americans. Carotenoids are yellow, orange, and red pigments synthesized by plants. The most common carotenoids are α-carotene, β-carotene, β-cryptoxanthin, lutein, zeaxanthin, and lycopene. Tomatoes are known to contain lycopene and allicin is present in garlic. Phytosterols include sterols and stanols with a similar chemical structure to cholesterol. A high concentration of phytosterols is found in plant products such as unrefined vegetable oils (including nut and olive oils), legumes, nuts, and seeds while modest amounts are found in cereal grains, fruits, and vegetables (Table 10). The most commonly occurring phytosterols in the human diet are β-sitosterol, campesterol and stigmasterol. The intake of naturally occurring phytosterols through diet ranges between ~150–450 mg/day. Several potential mechanisms have been proposed to explain the action of bioactive components present in vegetables and fruits (415,416). Phytochemicals compete with cholesterol for inclusion/absorption in micelles within the intestinal lumen and impact on cholesterol absorption (417).

POTENTIAL HEALTH BENEFITS

Fruits and vegetables rich in fiber or phytochemicals such as plant stanols and sterols may be helpful in lowering TC and LDL-C levels (418-420). Other reported health benefits include a lower risk of developing cataracts and age-related functional decline (406,408,409). Health benefits are reported to vary significantly depending on the type of bioactive components present, consumption quantity or intake levels and frequency of consumption. Four trials have examined fruit and vegetable consumption at 6 or 12 months (421-424). The pooled analysis (970 participants) showed no effect of the intervention on TC levels (425). Two trials over 12 months examining the effects of fruits and vegetables on LDL- C showed a small, non-significant reduction (421,424). No significant increase in HDL-C levels was seen (421,424,425). Three studies reported a slight but non-significant increase in TG (421,423-425).The Dietary Approaches to Stop Hypertension (DASH) study (426-429) examined the effect of a diet rich in fruits, vegetables, and low-fat dairy products on blood pressure and cholesterol levels, and reported a modest decrease in TC and LDL-C. HDL-C levels remain unaltered or decreased marginally, and no significant changes in TG were

observed. The net reductions in TC and LDL-C in men were borderline greater than in women by 0.27 mmol/L, or 10.3 mg/dL.

There are limited studies on individual fruit and vegetables and their effects on the lipid profile. Ravn-Haren et al. investigated the effect of whole apples, apple-pomace, and clear and cloudy apple juices (500 mL/day) on lipoproteins and blood pressure (430). They reported lower LDL-C levels by consumption of whole apple (6.7%), pomace (7.9%) and cloudy juice (2.2%), that LDL-C increased by 6.9% with intake of clear juice compared to whole apples and pomace, and that there was no effect on HDL-C, TG, weight, waist-to-hip ratio or blood pressure. A randomized controlled intervention trial to assess the effects of consumption of tomato-based foods on CVD risk factors showed no significant changes in TC, LDL-C, HDL-C or TG (431). In one meta-analysis it was noted that TC and LDL-C were not significantly different on low doses of lycopene levels, but both decreased by about 10% with high dose of lycopene (>25 mg day). There was no significant difference at either dose for HDL-C or TG levels (432). Finley et al. reported that pinto beans consumption lowered TC by ~8% in healthy individuals and by 4% in pre-metabolic syndrome subjects. Bean consumption lowered HDL-C concentration by 4% and LDL-C concentration by 8% (433).

Avocado contains a significant amount of oleic acid (MUFA) and phytosterols (e.g. β-sitosterol, campesterol) (434). As the avocado ripens, the fat ratios change with subsequent increases in unsaturated fats (MUFA > PUFA) and decreases in saturated fat. Results from clinical studies on the effects of avocado are mixed with an increase, a decrease or no effect on HDL-C noted (435,436). Some studies have suggested a limited TG-lowering effect with consumption of avocados (437,438).

The capsicum group of vegetables includes bell peppers, jalapenos, cayenne and other hot peppers. Capsicum contains many phytochemicals, including capsaicinoids (e.g. capsaicin, dihydrocapsaicin, capsiate), carotenoids (e.g. capsanthin, β-carotene), phenolics (hydroxycinnamic acids, coumaric and caffeic acid derivatives), quercetin glycosides and lignans. Studies on the capsicum group of vegetables have not found any clear clinical evidence of a lowering effect on TC or LDL-C levels. Eggplant and okra contain several bioactive phytochemicals compounds. While pre-clinical studies with eggplant seemed to suggest that some hypolipidemic potential, human studies have shown mixed results. Studies with extracts of eggplant do not appear to lower lipids (439-441). There is some recent but limited preclinical data suggesting that okra or okra extracts may lower LDL-C.

The cucurbitaceae family of vegetables (e.g. bottle gourd, snake gourd, pumpkins, butternut squash, acorn squash, summer squash, winter squash, cucumbers, bitter melon and chayote) is rich in carotenoids and other phytochemicals; however, it is unclear if the cortex from the fruits in the family has any effects on lipid profile. There is limited experience from clinical studies, although results from some pre-clinical studies suggest that pumpkin seeds may lower LDL-C concentration. Pre-clinical studies also suggest a lipid-lowering effect by bitter melon. Studies with cranberries show mixed results on HDL-C with some showing an increase and some

unchanged levels (442-447). Studies on blueberries are limited. In pre-clinical studies, consumption of blueberries led to alterations in plasma lipid concentrations (decreases in TC and LDL-C and increases in HDL-C) (448). However, there are few clinical studies on blueberries, and they seem to suggest there may be a modest effect on lowering LDL-C (449).

Several studies have indicated that phytosterols at higher doses can lower LDL-C concentration significantly. However, phytosterol intake at low doses, typically associated with food, may have less pronounced effects. The maximum LDL-C lowering efficacy is reported at an intake of approximately 3 g/day (24,450-452). In a recent review of 84 studies, Demonty et al. reported a dose-dependent LDL-C lowering effect of phytosterols and that a dose of 3 g/day lowered LDL-C by 11% (9% at a dose of 2 g/day) (452). Based on findings like these, the US National Cholesterol Education Program recommends a phytosterol intake of 2 g/day to enhance lowering of LDL-C concentration (24,450,451,453-457). In a meta-analysis that included 91,379 men, 129,701 women, and 5,007 CHD events, results demonstrated a 7% lower CHD risk for each additional fruit serving per day (415). CHD risk reduction was also evaluated as a part of nutritional recommendation interventional studies on vegetables and fruits (458,459).

SAFETY CONCERNS

Greater consumption of fruit juice has been associated with a higher risk of type 2 diabetes (460).

DIETARY GUIDELINES

A 2010 study found that the average consumption of fruits and vegetables in the U.S. was 3.6 servings (1.4 servings of fruits and 2.2 servings of vegetables) per person per day. The AHA recommends intake of at least 4 to 5 servings of vegetables and fruits (2 to 4 servings of fruits per day and 3 to 5 servings of vegetables) per day. Their current position is that fruits and vegetables in general contain nutrients that may help prevent heart disease. The AHA suggests that there needs to be more research done on the impact of individual phytochemicals (e.g. plant sterols, flavonoids, sulfur-based compounds) to better assess the claims on lowering individual cardiovascular risk factors. The 2010 Dietary Guidelines for Americans recommend that most people, based on a 2000-kcal diet, should consume at least 9 servings of fruits and vegetables per day (4 servings of fruits and 5 servings of vegetables).

Whole Grains

Whole grains include barley, brown rice, buckwheat, bulgur (cracked wheat), millet, oatmeal and wild rice. They contain macronutrients such as complex carbohydrates and protein as well as bioactive components such as fiber, vitamins, antioxidants, and trace minerals (461). Whole grains are defined by the American Association of Cereal Chemists International and the FDA as consisting of the “intact, ground, cracked or flaked fruit of the grain whose principal components, the starchy endosperm, germ and bran are present in the same relative

proportions as they exist in the intact grain", and they are an important source of fiber although levels can vary between sources (Table 12). For example, whole wheat contains the highest amount of fiber and brown rice contains among the least. Whole grains contain ~80% more dietary fiber than refined grains, as the latter are milled, a process that removes bran and germ. The refining process also removes bioactive components such as antioxidants, phytochemicals, and minerals. Refined grains include white flour, white rice, white bread and corn flower. Health benefits ascribed to whole grains are mainly due to the presence of fiber and bran. Carbohydrates present in the whole grains are digested very slowly due to the presence of fiber resulting in slow release of glucose. Further, soluble fiber decreases cholesterol levels by binding to bile acids in the gastrointestinal tract and increasing their excretion (383). Insoluble fiber helps move waste through the digestive tract.

Table 12. Fiber Content of Grains*

Food	Serving Size	Total Fiber/ Serving (g)	Soluble Fiber/ Serving (g)	Insoluble Fiber/ Serving (g)
Wheat bran	½ cup	12.3	1.0	2.7
Barley, pearled, cooked	½ cup	3.0	0.8	2.2
Oatmeal, dry	⅓ cup	2.7	1.4	11.3
Bread, pumpernickel	1 slice	2.7	1.2	1.5
Wheat flakes	¾ cup	2.3	0.4	1.9
Bread, rye	1 slice	1.8	0.8	1.0
Bread, whole wheat	1 slice	1.5	0.3	1.2
Rice, white, cooked	½ cup	0.8	trace	0.8
Bread, white	1 slice	0.6	0.3	0.3

* Adapted from Anderson JW. *Plant Fiber in Foods*. 2nd ed. HCF Nutrition Research Foundation Inc, PO Box 22124, Lexington, KY 40522, 1990.

POTENTIAL HEALTH BENEFITS

The consumption of whole grains has the potential to have beneficial cholesterol lowering effects. Health benefits seem to vary significantly depending on the type of grain, consumption quantity or intake levels and frequency of consumption. Results from randomized intervention studies of whole grains on blood lipid profile have been variable. However, findings regarding the efficacy of oat and barley β-glucan in lowering blood lipids are well substantiated. Similar benefits were observed with rye-based whole grain, red yeast rice, and buckwheat.

The impact of whole grains on lipid profile has been investigated in multiple trials and the results have been variable. A Cochrane review of nine RCTs that included 1,414 participants did not find a significant difference between whole grain vs. low whole grain/refined grain groups (462). One RCT investigated the impact of a 12-week intake of low-fat breakfast. Giacco et al. reported a significant 5% reduction in LDL-C concentration from consumption of whole grains (463). A systematic review of 64 studies with ready-to eat cereals noted that LDL reduction could be seen in ready to eat cereals with soluble fiber (464). Similarly, several studies including the ongoing the Grain Mark Study have shown significant reductions in LDL-C as well as of systolic blood pressure with whole grain intake (377,465-472).

The type of whole grain and amount of whole grain may have differential effects on lipid lowering. In a meta-analysis of nine studies, the consumption of whole grain appeared to result in a mild reduction in LDL-C (~3.47 mg/dL) and TC (~4.46 mg/dL; diet rich in whole grain oats had greater reduction of ~6.57 mg/dL) (473). Another trial that studied the impact of high intake of oats (70 g twice a day) reported that this oat rich diet could lower TC by 3.1% and LDL-C by 11.6% in Asian Indians (474). Another RCT reported that intake of 100 g of oats reported a reduction in both TC (~12.76 mg/dL) and LDL-C (~8.49 mg/dL) (475). A meta-analysis of trials with oats also supported the positive lipid lowering effects of oat β-glucan on LDL-C and non-HDL-C (396). The consumption of ancient grains, such as Khorasan wheat that are higher in soluble fiber, also appear to lead to the reduction in LDL-C and TC (476,477). Whole grain sorghum also appeared to lower TC (478). Some have suggested that rye-based whole grain foods were more effective in lowering TC levels compared with wheat-based foods (466). The consumption of high-fiber rye bread (9.3 g/day to 18.6 g/day fiber) enriched with nonesterified plant sterols (2 g/day to 4 g/day) in normocholesterolemic subjects resulted in reductions in TC (~5.1% to 6.5%) and LDL-C (8.1% to 10.4%) (479). Liu et al. analyzed the data from more than 90 randomized trials and found that red yeast rice reduced TC levels by 0.91 mmol/L (35 mg/dL), LDL-C by 0.73 mmol/L (25 mg/dL) and TG by 0.41 mmol/L (35 mg/dL), and increased serum HDL-C level by 0.15 mmol/L (5 mg/dL) (480). The types of rice appear to have variable effects on lipid profiles. The major active compounds in red yeast rice are monacolin K (or lovastatin) and related substances, all of which are HMG-CoA reductase inhibitors (481). Red yeast rice also contains sterols, isoflavones, and MUFA. There are several societies such as Health Canada, Whole Grains Council, FDA and German Nutrition Society that have given interim support to the claim that there are lipid-lowering effects of whole grains (482-485). In a RCT called the BRAVO study, a brown rice diet lowered TC and LDL-C in Japanese with metabolic syndrome (486). Another RCT noted there was no significant difference in TC and LDL-C between the consumption of brown rice vs. white rice (487).

In the Nurses' Health Study, women who ate whole-grain products regularly showed a 30% less risk for heart attack or cardiovascular mortality compared to women who ate whole grains less frequently (387). A recent meta-analysis of seven studies showed that CVD (heart attack, stroke or need for a cardiac intervention) was 21% less likely in subjects consuming 2.5 or more servings of whole-grain foods per day compared with those who consumed less than 2 servings per day (488,489). However, the European Food Safety Authority and American Society for

Nutrition have expressed some caution regarding claims for whole grains due to variability in definitions across studies (490). The potential mechanisms for whole grain health benefits have been postulated in several papers (491).

DIETARY GUIDELINES

The Dietary Guidelines for Americans recommends that individuals should reduce the intake of refined grains. They recommend that some refined grains should be replaced with whole grains with at least half of all grains should be whole grains (328). The Dietary Guidelines for Americans recommends that product labels with the words “whole” or “whole grain” before the grain ingredient’s name can be used to identify foods with whole grains (328). The AHA recommends 6 to 8 servings of grain foods a day with at least 3 or more whole grains per day. The 2005 Dietary Guidelines for Americans recommend that individuals should “consume 3 or more ounce-equivalents of whole grain products per day, with the rest of the recommended grains coming from enriched or whole-grain products. In general, at least half of the grains should come from whole grains.” The 2010 Dietary Guidelines for Americans continue to support these recommendations.

Fortified/Enriched Functional Foods

Humans consume 160-360 mg of phytosterols/day through diets rich in fruits and vegetables. It has been suggested that phytosterols (sterols and stanols) may be effective in the lowering of TC and LDL-C levels. Many fortified/enriched functional foods have been developed in the past 20 years. Examples include margarines, yogurt drinks, orange juice salad dressings, soy milk and fortifications with vitamins, minerals, and phytosterols. Most widely used phytosterols in functional foods are sitosterol, campesterol, and stigmasterol.

POTENTIAL HEALTH BENEFITS

The dose of plant sterols/stanols may have an impact of lipid profile. A consumption of phytosterols of 2-3 g/day with fortified functional foods may decrease TC and LDL-C concentrations by 10-15% (492-494). A phytosterol intake of 296 mg/d in the European Prospective Investigation into Cancer and Nutrition-the Netherlands (EPIC-NL) population was associated with mild reductions in TC (-0.06 mmol/L (2.3mg/dl) per 50 mg/d) and LDL-C (-0.07 mmol/L) (2.7mg/dl) (495). Some have reported that 2g/day of sterols/stanols leads to a 10% reduction in LDL-C even in trials with interventions lasting >6 months (496,497).

Several margarines fortified with phytosterols are presently available in the US. Several studies have been conducted to examine the benefits of fortified margarines (420,450,492,494,498-503). One study examined the effects of margarine fortified by sitostanol in patients with mild hypercholesterolemia (492), and showed that patients consuming the fortified margarine had a 10-14% decrease in TC and LDL-C concentrations while there was no

significant effect on HDL-C or TG concentrations (499). Another study involving the use of sitostanol-fortified margarine in postmenopausal women with CHD reported that there was a 13% and 20% decrease in TC and LDL-C concentrations, respectively (compared to a 5% decrease in women consuming unfortified margarine) (503). Margarine enriched with plant sterol esters (rapeseed or tall oil) that have 2 g of sterols/day can result in LDL-C reductions of 8-9% (504). Another study with a low fat spread with plant sterols (3 g/day) resulted in LDL-C reduction of ~0.26 mmol/L (10.1mg/dl) (505).

Plant sterols have also been added to drinks. A study of phytosterol supplemented milk and omega-3-supplemented milk noted that phytosterol supplemented milk had greater reductions in TC and LDL-C than omega-3-supplemented milk (506). In another study with phytosterols-enriched fermented milk, LDL-C reduction ranged from 0.15 mmol/L (5.9mg/dl) to 0.27 mmol/L (10.5mg/dl) (507).

Fortified-mayonnaise products containing phytosterols were reported to be very effective in lowering LDL-C concentration. Daily intake of mayonnaise containing 0.3, 0.4, and 0.5 g of phytosterols resulted in a 12%, 11% and 15% decrease in LDL-C concentration, respectively (494,508). In another study, consumption of 0.5 g of phytosterols lowered LDL-C concentration by 8% (509). Fortified-yogurt products containing phytosterols are relatively new to the market. A 10% decrease in LDL-C concentration was observed with fortified-yogurt containing 1.6 and 2.0 g of phytosterols (494,510). Results have been mixed and a smaller reduction of LDL-C concentration (4-6%) was observed with low-fat (2%) yogurts containing 1 g of phytosterols (511). In a meta-analysis of 33 studies published between 1998 and 2011, a 10% reduction in LDL-C concentration was reported with food matrix containing PUFA and MUFA. In addition, a >10% mean reduction in LDL-C concentration was seen when β-sitostanol and campestanol as well as stanol esters were used (494). The fortified functional foods examined in the latter study included margarine, mayonnaise, yogurt, milk, cheese, juice, and chocolate.

The impact of plant sterol supplementation along with lipid lowering therapies have also been studied. A study reported a reduction of TC (12% vs. 5% for placebo) and of LDL-C (17% vs. 7% for placebo) in subjects with an LDL-C concentration of ≥130 mg/dL on statin therapy (512). The addition of 2.0 g of plant sterols to statins resulted in greater reductions in TC and LDL-C (further reductions of ~7.7% and 6.5%, respectively) (513). A meta- analysis of 15 RCTs explored the impact of the combination of plant sterols and lipid lowering therapy. This study noted that the combination therapy resulted in greater reductions in TC (~0.30 mmol/L) (11.7mg/dl) and LDL-C (~0.30 mmol/L) (11.7mg/dl) (514). Some individuals may need to be on multiple lipid lowering medications to have plant sterols impact the lipid profile. One study noted that individuals with higher rates of synthesis of cholesterol (e.g. noted by lathosterol-to-cholesterol ratio) appear to be less responsive to plant sterols/stanols (515). Individuals with familial hypercholesterolemia needed to be on both simvastatin and ezetimibe and not simvastatin alone for plant sterol supplementation to be beneficial in familial hypercholesterolemia (516).

DIETARY GUIDELINES

The European Food Safety Association (EFSA) noted “A clinically significant LDL-cholesterol lowering effect of about 10% can be achieved by a daily intake of 2 g of phytosterols in an appropriate food (e.g. fat spreads). The magnitude of the cholesterol-lowering effect may differ according to the food matrix” (517). An advisory from the Nutrition Committee of the AHA reviewed the evidence on food containing plant sterol or stanol esters. They concluded that while they are a promising dietary intervention, these products should undergo longer term studies to assess if there are adverse effects. The AHA does not recommend routine by the general population and their use should be reserved for adults with hypercholesterolemia or an atherosclerotic event who require lowering of total and LDL-C levels (518).

Spices/Garlic

Garlic has been used as both food and medicine in many cultures for thousands of years. Garlic (Allium sativum) is a member of the Amaryllis (lily) family, related to onions, shallots, chives and leeks. The characteristic flavor and pungency of garlic are due to an abundance of oil- and water-soluble sulfur-containing elements, likely responsible for any medicinal effects ascribed to this plant. Allicin is unstable, and changes chemically during processing.

POTENTAIL HEALTH BENEFITS

Garlic has been advocated to lower TC concentrations and blood pressure, but results have not been consistent (503,519-522). A meta-analysis of 14 studies suggested that garlic can result in reductions in both TC and LDL-C (standardized mean difference of -1.26 and -1.07, respectively) (523). A randomized trial included 192 participants with LDL-C concentrations ranging from 130 to 190 mg/dL (3.36 to 4.91 mmol/L) and three different garlic preparations (raw, powdered, and aged garlic extracts) where patients were treated with a daily dose approximately equivalent to one 4 g clove for six months (6 days/week). The study found that none of the preparations of garlic had a significant effect on LDL-C or other lipid levels (524). Several other studies also suggest that there was no significant effect of garlic on TC or LDL-C concentration (520,521,524,525). Schwingshackl et al. evaluated multiple meta-analyses to better understand the impact of garlic on lipids. While many meta-analyses did suggest a positive impact of garlic on lipids, Schwingshackl et al. noted that it was difficult to reach a clear conclusion because of the substantial heterogeneity among the trials in the various meta-analyses (526).

SAFETY CONCERNS

Garlic can cause bad breath, a burning sensation in the mouth or stomach, heartburn, gas, nausea, vomiting, body odor and diarrhea. Side effects are often worse with raw garlic. There have been reports of bleeding after surgery in people who have taken garlic. Asthma has been

reported in people working with garlic, and other allergic reactions are possible. Garlic can irritate the gastrointestinal tract.

Beverages

TEA

Tea is consumed in different parts of the world as green, black or oolong tea. Western countries consume mostly black tea and Asian countries, mainly Japan and China, consume green tea and black tea. Oolong tea, which is produced by partial fermentations, is consumed mainly in southern China. Major components of tea include polyphenols (catechins), caffeine, amino acids, vitamins, flavonoids, polysaccharides and fluorine. Other constituents are carbohydrates and traces of minerals. Tea polyphenols are comprised largely of the epicatechin group of flavanols and catechins and their dimers (theaflavins) and polymers (thearubigins) have been identified as major tea polyphenols. Processing of black tea results in chemical changes and the oxidation process can lower flavonoids to <10%. Differences in flavonoid composition (e.g. relative levels of catechins and epicatechins and their oxidized condensation products) may result in differences in physiological effects between black and green tea.

Green and black tea may lead to mild reductions in TC and LDL-C. Green tea contains many catechins (e.g. epigallocatechin-3-gallate) that appear to influence lipid metabolism in animal models (e.g. potential increases in bile acid production and upregulation of LDL- receptors in liver, suppression of PCSK9) (527,528). The association between catechins and TC and LDL-C reduction in humans may have mild to moderate associations in human studies (529). In recent meta-analyses of RCTs, green tea was shown to have a mild reduction in TC (~5 mg/dL) and LDL-C (~7 to 9 mg/dL) levels (527,530). Some observational studies have reported that habitual intake of black tea is associated with relatively lower TC concentrations (531-533). However, clinical trials results evaluating the effects of black tea on TC have been inconsistent with some studies reporting no significant change in lipid profile of borderline hypercholesterolemic subjects (533-537). A meta-analysis, which evaluated the effect of consumption of black tea, reported that there was a mild reduction in LDL-C (~5 mg/dL) in healthy subjects but not those with established coronary artery disease (538). Meta-analyses have reported that green tea and black tea mildly reduced TC and LDL-C levels but did not find a significant effect on HDL-C or TG levels (539-541).

With regard to safety concerns, no significant side-effects or toxicity have been reported with green tea consumption. The stimulatory effect of green tea is less than that of coffee (542). A few cases of liver toxicity have been reported associated with consumption of large quantities of green tea or green tea extract. However, the incidence of this adverse effect is extremely low. Since green tea may interfere with the absorption of iron supplements, some have suggested that iron supplements should not be ingested together with green tea components (543). However, some studies did not find a significant correlation between green tea intake and iron levels (544).

COFFEE

Coffee, a complex chemical mixture, including caffeine, carbohydrates, lipids, amino acids, vitamins, minerals, alkaloids and polyphenols is one of the most widely consumed beverages in the world. Consumption of coffee may affect LDL-C concentration, and some studies have suggested that fat soluble molecules coffee (e.g. diterpenes such as cafestol and kahweol) can alter TC and LDL-C concentrations (545-548). Some studies have suggested that the levels of lipid altering molecules may be influenced by how coffee is prepared (greater amounts noted in preparations with boiled/unfiltered coffee and smaller amounts in brewed/filtered coffee) (549). Some have surmised that the filter (e.g. filter paper) may retain oil droplets containing diterpenes from ground coffee while unfiltered coffee allows for these oils to be present in the coffee.

In one meta-analysis, it was found that consumption of unfiltered, boiled coffee dose-dependently increased TC and LDL-C concentrations (23 mg/dL and 14 mg/dL, respectively), while consumption of filtered coffee resulted in only small changes (TC by 3 mg/dL and no effect on LDL-C concentration) (550). The Health Professionals Follow-up Study and the Nurses' Health Study cohort with 130,000 subjects reported filtered coffee did not impact TC, LDL-C and HDL-C levels (551). The consumption of >2 cups of coffee prepared through a pressure-based method (e.g. boiling water forced through a middle chamber that contains coffee grounds separated by a filter; the resultant coffee has limited exposure time to coffee grounds as in non-pressurized filtered coffee) did not lead to significant alterations in TC, LDL-C and HDL-C levels in an Italian Cohort (552). In a study from a Brazilian study cohort, the consumption of filtered coffee resulted in no alterations in TC, LDL-C and HDL-C levels (553). The differential effects from various coffee preparations on TC and LDL-C were also noted also in other clinical trials and meta-analysis (554-558). In another trial, coffee low in diterpenes did not result in alterations in TC, LDL-C and HDL-C levels (559).

COCOA PRODUCTS

Cocoa is rich in polyphenols. Cocoa is the non-fat component of finely ground cocoa beans that is used to produce chocolate (560). A meta-analysis examining the effects of flavanol-rich cocoa products or dark chocolate on the lipid profile reported that intervention with dark chocolate/cocoa products significantly reduced LDL-C and TC levels by about 6 mg/dL, respectively, with no statistically significant effects on HDL-C levels (561). The trend toward lowering of LDL (with various magnitudes of LDL-C reductions) was seen in other clinical trials or meta-analysis (562-565). In other trials, HDL-C levels were increased with chocolate consumption (564-567). A study found that combination of plant sterols with dark chocolate can lead to mild reductions in LDL-C concentration (568).

ALCOHOLIC BEVERAGES/WINE

The potential beneficial effect of wine intake on cardiovascular risk and mortality has been branded as the “French Paradox”, as lower rates of heart disease was observed in France despite a diet rich in butter and cheese. Several studies have been undertaken to explore any potential health benefits of wine. On balance, these studies suggest that CHD risk is lower by about 20-40% in individuals that consume low- to medium-quantities of wine compared to non-drinkers (569-571). Moderate alcohol consumption has also been associated with other health benefits such as better insulin sensitivity and reduced thrombotic risk (572). Wine contains a number of constituents beyond alcohol, such as sugars (glucose, fructose), other carbohydrates (pectins and glucans), organic acids (tartaric and malic acids), phytochemicals (phenolics, anthocyanins, tannins, resveratrol), nitrogenous compounds (proteins, amino acids and ammonium salts) and inorganic substances (potassium iron and copper salts). The phenolic content of a red wine generally varies between 1,000 to 3,500 mg/L Gallic Acid Equivalent (GAE). The highest concentrations of grape polyphenols are found in the skin, stems, and seeds. Although not fully understood, several explanations have been proposed to explain the lower risk of heart disease observed in individuals with low to moderate alcohol consumption. One plausible explanation is an increase in HDL-C levels (572), while other potential mechanisms involve the role of phytochemicals (572-574). Beyond reduction of LDL-C concentration, effects of phytochemicals include an improved endothelial function, lower blood pressure, inhibition of platelet aggregation, reduced inflammation and activation of proteins preventing cell senescence, e.g. sirtuin 1 (573).

Several studies have reported that people who drink wine in moderation have lower risk of heart disease, compared to those who do not drink wine (569,570,575). Several observational and clinical studies have reported strong positive relationships between wine consumption and HDL-C; an increase of HDL-C by about 12% was reported with one to two drinks per day (569,575-581). The degree of effect of wine on HDL-C seems to vary in other studies. In a study of individuals with T2DM, red wine increased HDL-C levels by ~2.0 mg/dL (582). In an analysis of 10,893 subjects from the Atherosclerosis Risk in Communities (ARIC) study, it was noted that low-to-moderate alcohol consumption resulted in mild reductions of TG, TC, LDL-C, sdLDL-C, and apoB levels and increases in HDL2-C (583). In another study, HDL-C did not increase with consumption of wine (584). The ability of alcohol to increase HDL-C levels consistently needs further exploration.

The effects of TG and TC with moderate alcohol intake is not consistent across studies. However, no clinical trial has provided solid evidence that alcohol could be used to increase HDL-C levels. Some studies showed increasing TG levels with alcohol consumption, likely due to the relatively high caloric level of alcohol (7 kcal/g) (585-587). Some studies have reported a positive association between alcohol and TC (588) while others found no such association (569). In a study of 3,897 individuals with metabolic syndrome in the PREDIMED, they found no clear association between red wine consumption (>1 drink/day) and TG levels (589). In one cross-sectional prospective study, the interrelationship between alcohol intake, cigarette smoking, body weight and blood lipid concentrations was examined (585). The study did not find an association between alcohol intake and TC levels, but a strong positive relation was

observed between alcohol consumption and HDL-C levels, and further, a significant increase in TG levels was observed in heavy drinkers. A meta-analysis of the effects of alcohol consumption (30 g/day) on blood lipids was conducted in people with no prior history of chronic disease and no history of alcohol dependence (590-594). Findings included an increase of HDL-C by about 4 mg/dL and of apoA1 by about 9 mg/dL, an increase in TG by about 6 mg/dL, and a decrease in fibrinogen by 7.5 mg/dL.

The relationship between alcohol consumption and prevalence of metabolic syndrome was investigated in Japanese men and women (578). The results of the study indicate an increase in HDL-C levels with increasing alcohol consumption. No significant change in TG was observed in light drinkers. Another study evaluated the association between alcohol consumption and blood lipid levels in hypertensive men and reported increases in HDL-C cholesterol and TG with an unchanged TG/HDL-C ratio with an increase in alcohol consumption [after adjusting for demographic and dietary factors in heavy (≥30 g/day) drinkers] (587). Elevated TG levels can be seen with excess alcohol intake. Alcohol consumption is thought to increase the level of fatty acid synthesis and decrease the degree of fatty acid oxidation, leading to increased hepatic VLDL TG secretion. The impact of alcohol intake on TG can vary between individuals due to genetic variability and amount of alcohol imbibed (595,596).

Excessive alcohol intake has substantial negative health effects, including risk of cirrhosis of the liver, hypertension, stroke, type 2 diabetes, cancer of the upper gastrointestinal tract and colon, risk of injury and tendency to violence. Excessive drinking over time is associated with increased body weight and can impair short-and long-term cognitive function. Breastfeeding women should be very cautious about drinking alcohol. The 2010 Dietary Guidelines for Americans suggested that if alcohol is consumed at all, it should be consumed in moderation up to one drink per day for women and two drinks per day for men and only by adults of legal drinking age.

Vitamins

Vitamins, in trace amounts, are needed to perform vital cellular functions. Vitamins A, D, E, K and CoQ10 are fat soluble vitamins, while vitamins B1 (thiamine), vitamin B2 (riboflavin), vitamin B3 (niacin), vitamin B6 (pyridoxine), vitamin B12 (cobalamin), folic acid, biotin, and panthenoic acid are classified as B complex water-soluble vitamins. As vitamins cannot be synthesized, the levels of vitamins in the body can vary and can influence maintenance of health and disease states. In this section, we focus on effects of vitamins on lipid metabolism.

WATER-SOLUBLE VITAMINS

Vitamin B1, thiamine, is water soluble, absorbed from the diet in the small intestine (jejunum and ileum) and transported bound to albumin. It has limited tissue storage and frequent dietary intake is required. Thiamine can act as cofactor for enzymes involved in amino acid and carbohydrate metabolism, and influences several pathways, including the conversion of

pyruvate to acetyl CoA, synthesis of thiamine pyrophosphate and thiamine monophosphate and indirectly affect transketolase activity and pentose phosphate pathway reactions. Some have suggested that thiamine could indirectly influence hexosamine pathway intermediates, potentially affecting lipoprotein lipase. However, there are no randomized clinical studies to suggest thiamine supplementation can improve LDL-C or TG levels.

Riboflavin (vitamin B2) is a water-soluble protein absorbed in the proximal small intestine. In the liver, kidney, and heart, riboflavin undergoes phosphorylation reactions and is converted to flavin mononucleotide (FMN) and flavin-adenine dinucleotide (FAD). Proteins that interact with FMN and FAD are considered flavoproteins, and FMN or FAD may also be part of coenzyme-flavin complexes. Flavins and associated proteins are involved in electron transfer reactions that catalyze oxidation-reduction reactions in various metabolic pathways including carbohydrate metabolism, energy metabolism, lipid metabolism, and amino acid metabolism. Flavins also play a role in fatty acid desaturation (e.g. fatty acid oxidation, beta oxidation) and formation of phospholipids (597). In addition, flavins can also play a role in vitamin metabolism (e.g. biosynthesis of ascorbic acid and conversion of vitamin K to its active form), another potential mechanism to affect lipid metabolism. However, riboflavin deficiency has not been reported to result in clinically significant LDL-C, HDL-C, or TG abnormalities. Further, there are no randomized clinical studies to suggest an impact of thiamine supplementation on LDL-C or TG levels.

Panthothenic acid (Vitamin B5) is a water-soluble vitamin present as a component of coenzyme A and involved in fatty acid synthesis. Animal studies report that low pantothenic acid can lead to increased TG, cholesterol, and LDL-C levels. (598,599). There are limited human studies on the effect of vitamin B5 on the lipid profile. To date, a mild reduction in TC and LDL-C is reported in two short studies (600,601).

Biotin is a water-soluble vitamin that acts as a co-enzyme in carboxylation reactions. Some of these reactions are carried out by enzymes that can affect lipid metabolism (e.g. acetyl CoA carboxylase, pyruvate carboxylase, propionyl CoA carboxylase). Biotin deficiency can lead to increased levels of propionyl CoA, potentially resulting in higher levels of odd-chain fatty acids and other defects in metabolism of long-chain fatty acids. While biotin deficiency can be present in patients with inborn errors of metabolism, biotin deficiency is rare as it is present in many types of food. In addition, biotin is produced in large quantities by gut bacteria, although biotin deficiency can occur during long-term parenteral nutrition. At present, any impact of biotin on lipids in individuals without biotin deficiency remains unknown.

In summary, vitamins B1 (thiamine), vitamin B2 (riboflavin), biotin or panthenoic acid have not been to affect levels of LDL-C, TG, or TC. While there is no evidence that supplementation with these will improve the lipid profile, it is important to be aware of daily recommended intakes. The recommended intake for thiamine is 1.1 mg/day for women and 1.2 mg/day for men, while corresponding numbers for riboflavin is 1.1 mg and 1.3 mg daily per RDA guideline. There is no

clear recommendation for the daily intake of pantothenic acid or biotin. There is no known toxicity due to excess intake of thiamine, riboflavin, pantothenic acid or biotin.

Vitamin B6, B12, and folic acid impact on lipid metabolic pathways although their effects do not seem to result in significant lipid profile changes.

The co-enzyme pyridoxal-5-phophate is the active form of vitamin B6 and its formation requires riboflavin. It plays a role in decarboxylation and transamination of amino acids, synthesis of niacin from tryptophan, neurotransmitter synthesis, gluconeogenesis, heme biosynthesis, sphingolipids and steroid hormone modulation. Through the synthesis of niacin from tryptophan, vitamin B6 indirectly affect VLDL metabolism and subsequently TG or LDL-C levels. It is suggested to indirectly influence cholesterol metabolism through advanced glycation and lipoxidation end-products (602-604). Animal models with vitamin B6 deficiency display mild hypercholesterolemia and treatment with vitamin B6 reduced cholesterol levels (605-607). Both in vitro and animal studies have noted that severe vitamin B-6 deficiency can affect PUFAs by altering metabolism of omega-3 fatty acids from linolenic acid form to the functional forms eicosapentaenoic acid and docosahexaenoic acid (608-611). It has also been noted that vitamin B6 deficiency can lead to elevations in plasma homocysteine partly through inhibition of cystathionine-β-synthase.

Studies in humans offer a mixed and incomplete picture regarding any benefit of vitamin B6 replacement with regard to cholesterol and PUFAs. Some studies noted mild cholesterol improvements in vitamin B6 deficient individuals (612-614). In individuals without vitamin B6 deficiency, no lipid lowering effect of vitamin B6 was noted (615). While there is some evidence that suggests vitamin B6 status could influence cholesterol metabolism, there is no clear consensus on any effect on cholesterol under normal vitamin B6 conditions. In one study on vitamin B6 deficiency, there appeared to be small decreases in n-3 and n-6 PUFA concentrations (616). However, another study did not show improvement in PUFAs with vitamin B6 replacement (617,618).

While both animal and human studies indicate that vitamin B6 deficiency can lead to the accumulation of S-adenosylhomocysteine and increased serum homocysteine levels, increases in TC, LDL-C, or TG levels are not reported and it has not yet been elucidated whether supplementation with vitamin B6 is effective for the primary prevention of CVD. In multicenter trials such as the Heart Outcomes Prevention Evaluation 2 Study (HOPE) and the Norwegian Vitamin trial (NORVIT), Vitamins and Thrombosis (VITRO) and in meta-analyses, vitamin B6 supplementation did not reduce the risk of recurrent major CVD events (e.g. myocardial infarction, stroke, sudden death) (619-623).

Vitamin B12 is important through demethylation from methyl-tetrahydrofolate (5MTHF) to homocysteine to form methionine, in turn converted to s-adenosylmethionine. Vitamin B12 deficiency classically can result in impaired formation of tetrahydrofolate, reduced methionine levels, and subsequently impaired synthesis of DNA and abnormal maturation of granulocytic

and megakaryocytic lineages due to inadequate conversion of deoxyuridylate to thymidylate. Clinically this can present as megaloblastic anemia.

Vitamin B12 is also important for the isomerization of methylmalonyl-CoA to succinyl-CoA, important for catabolism of odd chain fatty acids and cholesterol. In addition, vitamin B12 deficiency is thought to increase odd chain fatty acids and methylmalonic acid in tissues such as liver and neural tissue. This pathway has not been shown in animal models to affect the lipid profile. While a small number of studies have suggested a predisposition of maternal low vitamin B12 levels for higher offspring TC and LDL-C levels, there are no clinical trials in non-pregnant subjects that suggest that TC , LDL-C or TG can influenced by vitamin B12 (624,625).

Folic acid plays an important role in synthesis of DNA. Folic acid or folate is initially converted to tetrahydrofolic acid (THF) and subsequently to 5-MTHF, a substrate for the cobalamin-dependent process to transfer the methyl group to homocysteine. THF also plays an important role as a co-enzyme in the metabolism of amino acids (e.g. serine, tryptophan, histidine catabolism), and synthesis of purines and pyrimidines. Folate has not been shown to directly impact lipid metabolism.

Deficiencies in folate and vitamin B12 can have adverse effects. Cobalamin deficiency can lead to increased homocysteine and reduced methionine levels, impaired formation of THF, and impaired DNA synthesis. Folate deficiency can result in decreased DNA synthesis, decreased catabolism of some amino acids, increased homocysteine and reduced methionine levels. Methionine is indirectly required for conversion of phosphatidylethanolamine to phosphatidylcholine (PC), a component of VLDL particles. While higher homocysteine levels could impact PC levels and secondarily VLDL formation, it has not been shown to result in significant changes to serum lipids in animal models. In clinical studies (e.g. Nurses' Health Study) and meta-analyses, increased homocysteine levels were associated with increased cardiovascular risk (590,626,627). However lowering homocysteine levels with B vitamins and folate does not appear to reduce this risk (619,621,628-632).

NIACIN

Niacin (vitamin B3) is important for formation of nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP) that plays an important role in fatty acid synthesis. While nicotinamide is a common form of niacin, it does not have the lipid lowering properties of nicotinic acid. Nicotinic acid is thought to help modulate hepatic production of VLDL and several trials have shown that niacin can raise low HDL-C levels with reductions in TG, Lp(a), and, at higher doses, LDL-C levels (633-640).

The effect of niacin on reduction of CVD/atherosclerosis is less clear. In an early trial, the Coronary Drug Project, niacin was noted to influence the incidence of nonfatal MI and stroke (641,642). Further, combination studies with fibrates, colestipol, and statins noted some

reductions in progression of atherosclerosis/CV events (643-645). However, not all trials have shown reductions in CVD events. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High TG: Impact on Global Health (AIM-HIGH; simvastatin + ezetimibe + niacin vs simvastatin + niacin) trial and HPS2-THRIVE Collaborative Group (HPS2-THRIVE; simvastatin + ezetimibe + niacin /laropiprant vs simvastatin + niacin /laropiprant) did not show a significant decrease in composite of CHD death, nonfatal MI, ischemic stroke, or hospitalization for acute coronary syndrome.

Of the B complex vitamins only niacin appears to consistently affect the lipid profile. The Recommended Dietary Allowance (RDA) of vitamin B6 is 1.3 -1.7 mg daily for men and 1.3 -1.5 mg daily for women and dietary sources are cereals, beans, leafy green vegetables, fruits (e.g. papayas, oranges, cantaloupe) and poultry, and fish. Vitamin B12 is present in animal products and the Western diet can contain up to 5 to 7 µg of cobalamin per day. The RDA for is 2.6 µg/day, and a serum cobalamin level >300 ng/L is considered normal. The daily folate requirement for adults is estimated to be approximately 50 µg/day. Fortification of breakfast cereals, flour, etc. can add significant amounts of folic acid to the diet. The RDA of niacin is 16 mg daily for males, and 14 mg for females while the standard therapeutic doses vary from 1.5 to 4.5 g/day. It should be kept in mind that prescription extended-release niacin is generally considered to be pregnancy category C. The use of medication doses of niacin may be limited by poor tolerability due side effects such as flushing, pruritus, paresthesias, or nausea. Pretreatment with aspirin/NSAID may reduce the incidence of flushing and other complications.

FAT SOLUBLE VITAMINS AND VITAMIN C

Vitamin K a fat-soluble vitamin with at least two forms, vitamin K1 (phylloquinone or phytonadione) and vitamin K2 (menaquinones, including menatetrenone), is mainly transported in TG rich lipoproteins (e.g. chylomicrons) to the liver. While vitamin K is carried with lipoproteins, there is limited data on any influence on lipid metabolism. The metabolism of vitamin K appears to be partly dependent on other vitamins (e.g. vitamins B2 and B3).

Unlike vitamin K, vitamin A can affect lipid metabolism. Pro-vitamin compounds of vitamin A exist in several forms including retinols, retinals, retinoic acids, and the carotene family of compounds (e.g. β-carotene). Carotenoids such as retinol are transported through the lymphatic circulation in chylomicrons taken up by the liver. In plasma, vitamin A circulates bound to retinol binding protein (RBP). In small numbers, it can also be part of VLDL, LDL, and HDL complexes. Animal studies and in vitro studies have noted an association between vitamin A abnormalities and altered oxidative phosphorylation, protein synthesis, abnormalities in hormone production (e.g. synthesis of vitamin D or steroid hormones), and alterations in activity of various enzymes (e.g. 11β-hydroxysteroid dehydrogenase type 1, 11β-HSD1).

Studies in rats have shown that vitamin A deficiency result in increased cholesterol absorption. Using an in vitro model, RAR ligands were showed to influence ABC transporter G1 (ABCG1) expression and influence HDL-mediated cholesterol efflux from macrophages (646). Vitamin A

levels also influence the degree of TG accumulation in adipocytes and blood (647,648). Other in vitro and animal studies have suggested that there could be some increases in TG rich VLDL through other molecular pathways. However, studies in humans have not reported any clear relationship between vitamin A deficiency and lipid levels. However, treatment with oral isoretinoic acid may lead to mild elevations in TG levels (649,650). Further, in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study, β-carotene was associated an increased risk of CVD events in individuals without a history of MI (651). In the Women's Antioxidant and Folic Acid Cardiovascular Study, there were no improvements in cardiovascular events with vitamin A supplementation (629).

Vitamin C has been noted to affect different pathways involving lipid metabolism. Vitamin C includes several compounds that are generally referred to as vitamin C because of their similar biologic activities and serves as a co-enzyme in hydroxylation reactions (e.g. collagen synthesis, norepinephrine synthesis), carnitine synthesis and has anti-oxidant properties (e.g. can interact with glutathione, aid in the scavenging oxygen-derived free radicals). The anti-oxidant properties are important to stabilize other vitamins including vitamin E and folic acid. Older studies noted reductions in TC after vitamin C supplementation in individuals with low vitamin C levels (652-654). As ascorbic acid can serve as a co enzyme for cholesterol 7 alpha-hydroxylase, low ascorbate levels are thought to decrease the conversion of cholesterol into bile acids. However, increasing vitamin C in individuals with normal vitamin C levels does not appear to lower cholesterol.

The studies on vitamin C have largely focused on its anti-oxidative properties as studies have suggested LDL oxidation as playing a role in atherosclerosis. However, any mechanism by vitamin C is not fully understood (654-658) and studies in humans with vitamin C report conflicting results. Results from small studies suggest that vitamin C supplementation might improve cardiovascular outcomes (659-662). Others, including a NHANES III study, found that ascorbic acid levels were not independently associated with CVD prevalence (663,664). The Physicians' Health Study II evaluated the effects of vitamin C on primary prevention of CHD and found no significant effect on major cardiovascular events, total myocardial infarction, or cardiovascular mortality (665). Other studies such as the Heart Protection Study, the Women's Antioxidant Cardiovascular Study, and the GISSI prevention trial noted no reductions in mortality with vitamin C supplementation (310,666,667).

Vitamin E contains α, β, γ, and δ tocopherols and α, β, γ, and δ tocotrienols and is exclusively obtained from the diet and carried in chylomicrons. Many groups have attempted to understand the molecular effects of alpha tocopherol on the cardiovascular system and its implications for cardiovascular heart disease (668-673). In animal and in vitro studies, α tocopherol was noted to have anti-oxidative properties and appeared to lower the levels of oxidized LDL. Results also suggest that vitamin E lower ABCA1 activity in monocytes, indirectly decrease ox-LDL uptake in smooth muscle, and decrease hepatic activity of several important enzymes needed for cholesterol metabolism (e.g. HMG CoA reductase, 7-dehydrocholesterol reductase). It is also thought to protect PUFA in membranes and in plasma lipoproteins from peroxidation. There are

no studies in humans demonstrating that α-tocopherol can alter the lipid profile. While there are some initial studies suggesting that mixed tocotrienols may lower lipid levels, further studies are needed, and supplementation with α-tocopherol have not shown benefit for primary or secondary CVD prevention. While early epidemiologic studies suggested an association between dietary vitamin E and risk of CVD, studies exploring the relationship between vitamin E and CVD have reported inconsistent findings (674-676). Trials such as Heart Outcomes Prevention Evaluation (HOPE) study, GISSI-Prevenzione trial, Physician Health Study–II and others did not show reductions in primary and secondary CVD events (310,665,677,678). Meta-analyses have also not found a decrease in cardiovascular events (679). In addition, some studies suggested that vitamin E supplementation may have adverse effects such as increased stroke and CHF risk (680,681).

While the interest in vitamin C's and E's antioxidant properties led to extensive research on lipid metabolism, there is now new focused interest in the effect of vitamin D. Vitamin D may exist in the form of vitamin D2 or D3. Vitamin D2 (ergocalciferol) derives from UV irradiation of ergosterol (found in plants and fungi). Vitamin D3 (cholecalciferol) is produced by the UVB irradiation of 7-dehydrocholesterol in the skin. Based on in vitro and animal studies, some have suggested that vitamin D could reduce intestinal absorption and synthesis of lipids, reduce cholesterol levels by inhibiting bile acid synthesis, and alter lipid metabolism. In addition, some in vitro and animal studies have suggested that higher levels of vitamin D may influence vascular calcification through reduced parathyroid hormone (PTH) and higher Klotho protein levels (a protein functioning as an FGF23 co-receptor). However, these suggested mechanisms still need to be studied closely.

The effect of vitamin D on serum lipids in humans appears varied and any mechanisms need to be elucidated. Randomized trials that examined the effect of vitamin D supplementation on serum lipids have found varied results. In some observational studies, lower vitamin D levels were associated with mildly higher TC, LDL-C and TG levels (682-685). Higher vitamin D levels were associated with relative reductions in LDL-C, TG and TC (684-687). In another trial, vitamin D had a mild lipid-lowering effect in statin-treated individuals (688). However, results regarding vitamin D replacement and lipid levels have not been consistent (682,683). In short term trials with a single dose or periodic replacements of vitamin D, variable improvements in the lipid profile were seen with very few studies showing improvements in LDL-C and TG (682,689-692). In longer term studies (≥6 months) with periodic replacement, there were no significant changes in lipid profile (692,693). In other trials in individuals with daily supplementation, no significant changes in TC, TG, HDL-C, or LDL-C were seen (472,694-698). Further, a meta-analysis noted that vitamin D supplementation had little effect on the lipid prolife (699). Another meta-analysis noted that vitamin D resulted in increases in LDL-C in obese subjects but not in non-obese subjects (700). The relationship between vitamin D and lipids in humans is not fully understood and more studies are needed to clarify the effect of vitamin D on lipids.

Dietary recommendations for fat soluble vitamins and vitamin C are evolving. There is a lack of consensus on a suitable endpoint or biomarker of adequacy for Vitamin K with greater variations in recommendation in the range for adults from which to base recommendations. The AI for vitamin K was suggested to be 90 µg/d for women and 120 µg/d for men (Institute of Medicine (US) Panel on Micronutrients 2001). A daily intake of 625 to 630 µg for men and 500 - 550 µg for women is recommended for vitamin A (www.nap.edu). The RDA for ascorbic acid is 75 mg per day for most women and 90 mg per day for men. For vitamin D the RDA is 600IU for individuals below 70 years of age and 800 IU for those above.

Summary

Functional foods are foods or food components that have the potential to provide disease preventing and/or health promoting benefits in addition to nutritional properties. They generally contain basic nutrients such as carbohydrates, proteins and/or fats and bioactive components, including dietary fiber, healthy fats (e.g. PUFA, MUFA), and antioxidants. Clinical studies conducted on some functional foods over past two decades have indicated that they may be useful in preventing, reducing and/or treating risks associated with CVD, diabetes, obesity, blood pressure or lipid disorders. Benefits seem to vary significantly depending on the type of bioactive components present in the functional foods, on the consumption quantity/intake levels and the frequency of consumption. Health benefits related to lipid disorders of some functional foods are summarized below.

Cold water fish such as sardines, anchovies, tuna, salmon, and trout, and fish products such as fish oil can reduce TG levels. A 20-40% reduction in TG was observed mainly when fish or fish oil is consumed in high doses. No significant changes in LDL-C or TC were reported. Consumption of nuts such as walnuts and almonds and seeds such as flax seeds may lower TC and LDL-C and improve the LDL-C/HDL-C ratio in healthy subjects or patients with moderate hypercholesterolemia. Nuts had no significant or minimal effect on reducing TG or increasing HDL-C concentration. Health benefits of nuts and seeds vary significantly depending on the type and nutrient composition and quantity consumed. Caution should be advised as to the possibility of developing allergic reactions to nuts. Soluble fibers such as psyllium, pectin, wheat dextrin and oat bran have been reported to reduce TC and LDL-C by about 10-15% if taken as per recommended amounts. No statistically significant reduction in TG levels was seen. Some insoluble fibers bind minerals such as calcium, magnesium, phosphorous and iron. A high fiber intake can cause abdominal discomfort, gas and diarrhea. The consumption of whole grains, instead of refined grains, may be more beneficial for lowering TC, LDL-C, or TG levels. The effects on lipid levels depend on the type of grain, and quantity of consumption. While there is strong evidence regarding the efficacy of oat and barley in lowering blood lipids, this is variable evidence for other cereal. Health benefits of whole grains are mainly due to the presence of fiber and bran. It is recommended to follow dietary guidelines regarding the quantity of grains consumed. An excess intake of grains can lead to increased weight and TG levels.

Clinical evidence on the effects of fruits and vegetables on cholesterol levels is mixed. Some vegetables showed positive effects and some others showed insignificant effects. Fiber-rich fruits and vegetables such as apples, pears, and beans were found to be helpful in modestly lowering TC and LDL-C concentrations. Avocados and olives that contain MUFA can assist in lowering lipid levels. Fruits and vegetables containing phytochemicals (e.g. berries) may also help to reduce cholesterol. The consumption of adequate quantities of beans can lower serum TC by ~8% in the normal individuals. Margarines, orange juice, and yogurt drinks with added plant sterols and/or stanols can reduce LDL-C levels by >10%. Some beverages such as tea, coffee, cocoa, or wine have been suggested to provide health benefits when consumed in limited quantities, probably due to the presence of phytochemicals such as polyphenols.

The subject of functional foods is in a relative infancy. Further clinical studies are needed to assess potential health benefits of foods where diet-health relationships are not sufficiently established. Importantly, intake of functional foods should not serve as a substitute for less than optimal eating habits or life style or be seen as the sole pathway to reduce a genetically inherited susceptibility to cardiovascular risk.

EFFECT OF WEIGHT LOSS DRUGS AND BARIATRIC SURGERY

Background

Obesity is a multifactorial, chronic disease involving metabolic, genetic, behavioral and environmental components, associated with impaired quality of life and a large number of life-threatening disorders, such as diabetes, CVD, metabolic syndrome, liver disease and cancer (701-703). The frequency of obesity has been increasing at an alarming rate over the past two decades and obesity is now recognized as a global epidemic, affecting over a half billion adults worldwide (704). Further, obesity is associated with a substantial increase in morbidity and premature mortality, responsible for more than 3.4 million adult deaths per year and global health cost equivalent to 2.8% of the world's GDP, or approximately US$2 trillion (705). According to World Health Organization (WHO) data, in 2014, 39% of men and 39% of women aged 18+ were overweight (BMI ≥25 kg/m^2) and 11% of men and 15% of women were obese (BMI ≥30 kg/m^2) (704). In addition, there has been a substantial increase in childhood, as according to the Center for Disease Control and Prevention (CDC), the prevalence of childhood obesity has more than doubled, and among adolescents quadrupled in the past 30 years (706,707). In 2011-2014, prevalence of obesity among children and adolescents (aged 2-19 years) in the US has remained relatively stable (708). Although obesity is thought to be a predicament of Westernized countries, it is also rising in developing countries. This may reflect drastic societal changes over the last two decades that have created an environment promoting a sedentary lifestyle and a high-fat and energy-dense diet. Globally, according to WHO, in 2016 the prevalence of obesity was highest (28.6%) in the Americas and (23.3%) Europe and lowest (4.7%) in South East Asia (704). A recent analysis based on 2015-2016 data from the National Health and Nutrition Examination Survey (NHANES) published in 2017 demonstrated that the prevalence of obesity in the US continues to be high, affecting 36% of US adults and 17% US

children and adolescents (708). However, according to NHANES data, the overall prevalence of obesity among young as well as among adults did not change from 2003-2004 through 2013-2014 (708,709).

BMI is generally used for classification of overweight and obesity, as direct body fat measurement is difficult (701,710,711). WHO recently published international standards for classifying overweight and obesity: a person with BMI ≥25 kg/m^2 is considered “overweight,” and a person with a BMI ≥30 kg/m^2 is considered “obese”, further subdivided on the basis of the severity of the obesity (712). However, these BMI criteria should be used with caution, as some Asian populations show remarkably different obesity related characteristics and are reported to be prone to the complications of obesity at lower BMIs (713,714). Waist circumference (WC) is also used as a risk indicator supplementary to BMI; it measures the regional distribution of excess body fat, i.e. visceral or intra-abdominal obesity. However, there is a high correlation of WC with BMI.

Obesity Treatment Strategies

In 1998, the National Heart Lung and Blood Institute (NHLBI) in cooperation with the National Institute of Diabetes and Digestive and Kidney Diseases, released the “Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—The Evidence Report” (715). An updated guideline from AHA/ACC/TOS for the management of overweight and obesity in adults was released in 2013 (716). Given that obesity is a chronic disease requiring lifelong intervention, treatment strategies should be framed into a concept of a stepwise intensification of care approach for weight management. Thus, typically, patients select treatment options, ranging from commercial to medical and surgical approaches, they feel most comfortable in trying. In the long term, prevention of obesity through education and changes in the obesogenic environment is essential. Lifestyle modifications remain the cornerstone of weight management, and has three components, diet, physical activity, and behavior modification (717). According to the NHLBI algorithm for treatment of obesity, a comprehensive program of lifestyle modification is recommended for all individuals with BMI ≥30 kg/m^2, or those with a BMI ≥25 kg/m^2 and risk factors for CVD (716). Although these lifestyle intervention programs have been shown to be effective in reducing weight in the short and medium term (718,719); over time, participants tend to gradually regain much of their lost weight (705,720).

An approach to consider pharmacological treatment of obesity should only be considered after dietary, lifestyle and behavioral interventions have been appropriately tested and their effect assessed. In the clinical setting, if a patient fail to induce or maintain a weight loss of 10% after 3 months of supervised medical weight management by lifestyle modifications, then addition of pharmacotherapy can be considered (717,721). Pharmacological treatment approach should only be used in conjunction with healthy lifestyle changes, including an increase in daily activity and a calorie-deficit diet. Currently, the following seven categories of medications can be used short-term in the treatment of obesity: sympathomimetics, drugs that alter fat metabolism, antidepressants, serotonin receptor agonists, antiepileptic drugs, antidiabetes drugs and

polytherapies. The clinician should be familiar not only with the basic principles regarding the pharmacotherapy of obesity but also consider regulatory and metabolic disturbances involved in the pathogenesis of obesity. Further, the selected pharmacological agent should exhibit minor, ideally none, side effects, be easy to administer for long-term use, be widely accessible and available at an affordable price. The goal of treatment is not only weight loss per se, but also improvement of obesity-related comorbidities, such as hyperglycemia, hyperlipidemia, and heart disease and ultimately improvement in quality of life. It has been demonstrated that sustained weight loss of 5-10%, achieved by current medication options, would result in health gain. However, few patients regard this as a successful weight loss outcome. Therefore, pharmacological agents should not be viewed as a remedy for obesity treatment. For patients with severe obesity and who meets specific indications, as described in details below, bariatric surgery can be considered. Pharmacotherapy can also be considered as adjunct to bariatric surgery when additional weight loss is required or to prevent weight regain after weight loss surgery.

Pharmacological Treatment Options

Pharmacotherapy of obesity is only one tool in a clinician's toolkit. In general, pharmacological treatment options should only be used as an adjunct to lifestyle intervention if the patient is not able to achieve the weight goal by lifestyle alone and meets the indications for drug therapy (722). In 2007 the US Food and Drug Administration (FDA) released an updated Draft Obesity Drug Guidance for the purpose of facilitating development of obesity drugs for medical weight loss, defined as a long-term reduction in fat mass with a goal of reduced morbidity and mortality through quantifiable improvements in biomarkers such as blood pressure, lipid levels, and HbA_{1c} (723). Thus, according to the guidelines, pharmacotherapy is approved for patients with a BMI ≥30 kg/m^2 or ≥27 kg/m^2 when complicated by weight-related comorbidities. Interestingly, 2007-2008 NHANES survey data demonstrated that only 2.2% of individuals who are obese are being treated by prescription medication.

Recently, as outlined below, four new medications were approved by the FDA, lorcaserin (Belviq, Arena Pharmaceuticals and Eisai Pharmaceuticals, San Diego, CA) and phentermine/topiramate extended release (Qsymia, Vivus, Inc, Mountain View, CA, USA) in 2012, and naltrexone/ bupropion (Contrave, Orexigen, Inc, La Jolla, CA, USA) and liraglutide (Saxenda, Novo Nordisk, Inc, Plainsboro, NJ, USA) in 2014. All these medications met the 2007 FDA Draft Obesity Drug Guidance and were approved with a requirement to conduct a post-marketing long-term cardiovascular outcomes trial. Prior to 2012, the only weight loss medicine on the market for long-term use was Orlistat, approved by the FDA in 1999 as the first lipase inhibitor for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet (724). Orlistat was approved as an over-the-counter medication in the US in 2007 at half the prescription dose due to its safety profile.

Sibutramine (Meridia), a norepinephrine and serotonin reuptake inhibitor, was approved in 1997 for weight management for patients who are unable to lose weight by diet and exercise alone. However, it was withdrawn from the market in Europe and the USA for safety concerns in 2010 based on data from the Sibutramine Cardiovascular Outcomes Trial (SCOUT) (725). In the SCOUT trial, the risk of primary outcome events (nonfatal infarction and stroke) was significantly increased in the sibutramine group as compared with the placebo group. Another centrally acting antiobesity drug, rimonabant, a cannabinoid CB1 receptor antagonist, has been suspended on the European market by the European Medicines Agency (EMA) in October 2008 due to serious psychiatric problems. These recent withdrawals of obesity drugs from the market due to safety issues have impacted regulatory and marketing policies for the development, registration and commercialization of novel drugs for weigh management, as the US FDA and the European EMA now request post-marketing studies to assess effect of a drug on the risk of cardiac events.

Drugs for Treatment of Obesity

ORLISTAT (XENICAL/ALLI)

Orlistat was launched in the European Union in 1998 under the trade name Xenical (Roche, Nutley, NJ, USA), later in April of 1999 it was approved by the US FDA for obesity management, including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. In addition, it was approved for use in more than 15 countries in Europe, South America, Southeast Asia and the Pacific region (726). In February, 2007, a lower dose formulation of orlistat under the trade name Alli (GlaxoSmithKline, Philadelphia, PA, USA) was approved by the US FDA for over-the-counter (OTC) use (727). The prescription form Xenical is available in 120 mg capsules to be administered thrice daily with the main meals, the OTC form Alli is available in 60 mg capsules that are also to be administered thrice daily with the main meals.

Orlistat is a selective and reversible inhibitor of gastric pancreatic lipase. It is a chemically synthesized derivative of lipstatin, a natural product isolated from the bacterium *Streptomyces toxytricini.* Its therapeutic activity takes place in the lumen of the stomach and small intestine. Orlistat inhibits lipase activity by forming a covalent bond with the active serine residue site of these enzymes and thus preventing the hydrolysis of TG from dietary fat to absorbable fatty acids and monoglycerides. Undigested TG are excreted in the feces, resulting in an inhibition of dietary fat absorption of 30% at an orlistat dose of 120 mg three times daily.

Orlistat: Clinical Trials- Effect on Lipids:

Orlistat is the most extensively studied pharmacological agent currently available for weight management. Since its release in early 1990s, there have been over 150 published clinical trials of its use on its own or in combination with other medications (728). The safety and efficacy of orlistat has been evaluated in numerous randomized double-blind, placebo-controlled trials (729-745). Among these trials, four trials lasted at least 2 years (730-733). The longest trial of

orlistat that evaluated its efficacy in the prevention of diabetes in obese patients, XENDOS, lasted 4 years (740). All these studies were conducted in conjunction with some kind of diet restriction. In some studies, patients were maintained on a hypocaloric diet for the first year and a eucaloric diet the second year (730-733), while other studies had 2- to 4-week placebo- or diet-alone run-in period (741-743). The primary endpoint for most studies was body weight reduction and the studies used the intent-to-treat approach for analysis. In these trials, patients receiving orlistat lost significantly more body weight, although the amount of weight loss was modest. In the 4-year XENDOS study in Sweden, 3,305 obese patients were randomized to either orlistat or placebo three times daily with meal (740). Mean weight loss after 4 years was significantly greater with orlistat than placebo (5.8 kg vs. 3.0 kg; P<0.0001). More orlistat-treated patients completed the trial (52% vs. 34% placebo; P<0.0001), despite the greater rate of GI events in the former group. After 4 year of treatment, the cumulative incidence of diabetes was 6.2% with orlistat and 9.0% with placebo, corresponding to a risk reduction of 37.3% (P=0.0032). Chanoine et al. studied the safety and efficacy of orlistat in weight management of adolescents in a 54-week trial (741). At the end of the study, BMI was noted to significantly decrease by 0.55 kg/m^2 with orlistat, but increased by 0.31 kg/m^2 with placebo. There have been a number of meta-analyses and systematic reviews of use of orlistat in weight management (746-759). In a meta-analysis of 11 placebo-controlled trials lasting at least 1 year in 6,021 overweight or obese patients, orlistat-treated patients lost 2.9% weight (95% CI 2.5 to 3.4%) (750). Further, the number of patients achieving ≥5% and ≥10% weight loss was 21% (19-24%) and 12% (8-16%) greater with orlistat than with placebo. In a recent analysis that included 15 placebo-controlled orlistat trials, the percentage of patients who achieved ≥5% weight loss at 1 year ranged from 35% to 73% and the proportion losing ≥10% ranged from 14% to 41%, significantly greater for patients taking orlistat than placebo (759). At the end of a second year of treatment when a weight-maintenance diet was prescribed, patients treated with orlistat 120 mg lost ~3.3% more of initial weight, and patients treated with orlistat 60 mg had lost ~2.5% of initial weight more compared to those treated with placebo.

Orlistat have been reported to produce favorable effect on plasma lipid levels. Due to the effect of orlistat to decrease absorption of dietary cholesterol, large randomized, placebo-controlled trials have consistently found orlistat to have a beneficial effect on total and LDL-C levels. In a meta-analysis of studies that enrolled patients with and without dyslipidemia and T2DM, a modest placebo-subtracted reduction in total [0.28-0.37 mmol/L (10.8-14.3 mg/dL)] and LDL [0.22-0.30 mmol/L (8.5-11.6 mg/dL)] cholesterol were seen in patients treated with orlistat. Furthermore, in a meta-analysis of 15 studies with 10,995 subjects, a significant decrease in TC levels in orlistat-treated patients correlated with mean weight reduction (r=0.48; P<0.05). However, when analysis were performed adjusting for weight loss, the reduction in TC correlated with orlistat treatment, suggesting cholesterol lowering effect of orlistat was independent of weight loss (758). Improvements in TC and LDL-C has been also reported in two post-marketing safety studies of orlistat, XXL (Xenical ExtraLarge) and X-PERT trials, irrespective of the magnitude of dietary restrictions prescribed to patients (760,761). In most studies, changes in TG levels were not significantly different from baseline, however in some

studies, orlistat treatment resulted in a modest, but statistically significant decrease in TG levels. In the majority of the trials, no beneficial effect of orlistat on mean HDL-C levels has been found.

Orlistat- Safety and Side Effects:

Generally, orlistat is well tolerated and the reported frequency of overall adverse events in clinical trials is similar to that in placebo-treated patients. The most commonly reported adverse effects among orlistat users are gastrointestinal disturbances including loose and/or fatty stools, flatus with discharge, fecal urgency, abdominal pain, nausea/vomiting, and fecal incontinence. Their incidence increases with increasing dietary fat intake and may be reduced by addition of psyllium fiber. The majority of adverse events were reported as being transient, mild to moderate in severity, usually occurring early in treatment, and generally resolving without intervention within the first few weeks. Due to its ability to reduce the absorption of dietary fat, orlistat use is associated with risk of reducing the absorption of fat-soluble vitamins, and people receiving orlistat are recommended to take fat-soluble vitamin supplementation.

LORCASERIN (BELVIQ)

Lorcaserin, was approved on June 27, 2012 by the U.S. FDA, under the trade name Belviq (Arena Pharmaceuticals and Eisai Pharmaceuticals, San Diego, CA) for long-term treatment for obesity in adults with a BMI ≥30 kg/m^2 or with a BMI ≥27 kg/m^2 and the presence of at least one weight-related comorbidity (762). It was the first anti-obesity drug approved by the FDA since Orlistat in 1999. Two previously approved non-selective serotonergic agents, fenfluramine and dexfenfluramine, were removed from the market due to heart valve damage (763). Lorcaserin selectively targets the 5-HT_{2C} receptor, but not 5-HT_{2B} receptors expressed on cardiac valvular cells (764). Although the exact mechanism of action is unclear, lorcaserin is thought to promote satiety and reduce consumption of food by selectively activating 5-HT_{2C} receptors located on anorexigenic pro-opiomelanocortin neurons in the hypothalamus. Belviq is prescribed at 10 mg twice daily.

Lorcaserin: Clinical Trials- Effect on Lipids:

Lorcaserin has undergone 3 major phase III clinical trials to assess efficacy and safety prior to FDA approval (Table 13). In two studies, called BLOOM (Behavioral Modification and Lorcaserin for Overweight and Obesity Management) and BLOSSOM (Behavioral Modification and Lorcaserin Second Study for Obesity) (765,766), volunteers who were obese or had a BMI ≥27 kg/m^2 with one comorbidity were enrolled. The third study, called BLOOM-DM (Behavioral Modification and Lorcaserin for Overweight and Obesity Management in Diabetes Mellitus), enrolled diabetic patients with HbA_{1c} 7-10% and a BMI of 27-45 kg/m^2 (767).

Table 13. Lorcaserin Phase III Clinical Trials

	BLOOM	**BLOSSOM**	**BLOOM-DM**

Study-group assignment	Lorcaserin 10 mg BID (n=1,595) Placebo (n=1,587)	Lorcaserin 10 mg BID (n=1,602) Lorcaserin 10 mg QD (n=801) Placebo (n=1,601)	Lorcaserin 10 mg BID (n=256) Lorcaserin 10 mg QD (n=95) Placebo (n=252)
Age at baseline (yr)	43.8/44.4	43.8/43.8/43.7	53.2/53.1/52.0
Weight at baseline (kg)	100.4/99.7	100.1/99.8/100.5	103.7/106.0/102.6
BMI at baseline (kg/m^2)	36.2/36.2	36.0/35.8/35.9	36.1/36.1/35.9
Study duration	52 week	52 week	52 week
Primary endpoints	Proportion of patients achieving ≥5% BW reduction at the end of year 1; change from baseline in BW; proportion of patients achieving ≥10% BW reduction at the end of year 1.		
Secondary endpoints	Changes from the baseline values for lipids (TC, LDL-C, HDL-C, TG), glycemic variables (fasting glucose, fasting insulin, HbA_{1c}, HOMA-IR), physical measures (waist circumference, BMI, SBP, DBP), inflammatory markers of cardiovascular risk (high-sensitivity C-reactive protein, fibrinogen) and the quality of life.		
Patients completing the study (%)	Lorcaserin: 883 (55.4%) Placebo: 716 (45.1%)	Lorcaserin (BID): 917 (57.2%) Lorcaserin (QD): 473 (59.0%) Placebo: 834 (52.0%)	Lorcaserin (BID): 169 (66.0%) Lorcaserin (QD): 75 (78.9%) Placebo: 157 (62.1%)
Patients achieving ≥5% weight loss (%)	Lorcaserin: 47.5% Placebo: 20.3%	Lorcaserin (BID): 47.2% Lorcaserin (QD): 40.2% Placebo: 25.0%	Lorcaserin (BID): 37.5% Lorcaserin (QD): 44.7% Placebo: 16.1%
Patients achieving ≥10% weight loss (%)	Lorcaserin: 22.6% Placebo: 7.7%	Lorcaserin (BID): 22.6% Lorcaserin (QD): 17.4% Placebo: 9.7%	Lorcaserin (BID): 16.3% Lorcaserin (QD): 18.1% Placebo: 4.4%
Weight change (kg)	Lorcaserin: -5.8±0.2 Placebo: -2.2±0.1	Lorcaserin (BID): -5.8±6.4 Lorcaserin (QD): -4.7±6.4 Placebo: -2.9±6.4	Lorcaserin (BID): -4.7±0.4 Lorcaserin (QD): -5.0±0.6 Placebo: -1.6±0.4

Lipids, % change from baseline (Lorcaserin 10 mg BID vs. placebo)	TC: -0.9 vs. 0.6; P=0.001 LDL-C: 2.9 vs. 4.0; P=0.049 HDL-C: 0.1 vs. -0.2; P=0.72 TG: -6.2 vs. -0.1; P<0.001	TC: -0.7 vs. 0.0; NS LDL-C: 0.3 vs. -0.1; NS HDL-C: 3.7 vs. 1.3; P<0.001 TG: -4.3 vs. -0.9; P=0.02	TC: -0.7 vs. -0.1; P=0.714 LDL-C: 4.2 vs. 5.0; P=0.802 HDL-C: 5.2 vs. 1.6; P=0.005 TG: -10.7 vs. -4.8; P=0.054

NS, not significant

The BLOOM trial, a phase III double blind placebo controlled trial, included 3,182 overweight or obese adults randomized to lorcaserin 10 mg or placebo twice daily for 12 months (765). Patients were placed on a reduced calorie diet with an intake of 600 kcal below the individual estimated daily energy requirements and instructed to exercise moderately for 30 min per day. Patients who completed the first 12 months of the study (55.4% of lorcaserin and 45.1% of placebo) were eligible to continue in the study for a second year - they were re-randomized to either placebo or lorcaserin. All patients received diet and exercise counseling at the initiation of the trial and at each subsequent follow-up visit at 2 weeks, 4 weeks and monthly thereafter. The primary endpoints at the end of year 1 were reduction of body weight by 5% or more, change in weight between baseline and the end of year 1, and the proportion of patients with a reduction in baseline body weight by 10% or more at the end of year 1. At 1 year, patients in the lorcaserin group lost an average of 5.8% of the baseline body weight compared with a 2.2% loss in the control arm. In the treated group, 47.5% achieved the weight-loss goal of ≥5%, compared to 20.3% of patients receiving placebo; further more patients in the lorcaserin group (22.6%) achieved ≥10% goal compared to patients in the placebo group (7.7%). Patients who received lorcaserin in both years had lower body weight than patients who received placebo and also lower body weight than patients who received lorcaserin in year 1 and placebo in year 2.

From a metabolic standpoint, at the end of year 1, compared with placebo, lorcaserin treatment was associated with significant decreases in WC, BMI, fasting glucose, insulin, the homeostasis model assessment of insulin resistance (HOMA-IR), and glycated hemoglobin. However, glucose and fasting insulin levels tended to increase with body weight during year 2. In terms of lipids, significantly greater reduction in TC (-0.90% vs. 0.57%; P=0.001) and TG levels (-6.15% vs. -0.14%; P<0.001) were observed in the lorcaserin than in the placebo group at year 1, but levels increased in both groups by the second year. The percentage change in LDL-C levels increased to a lesser extent in the lorcaserin compared to the placebo group (2.87% vs. 4.03%; P=0.049). In patients who received lorcaserin during year 1, but switched to placebo during year 2, levels of TC, LDL-C and TG tended to increase to the levels similar to the placebo group by year 2.

The BLOSSOM trial was a 52-week, randomized, double-blind, placebo controlled trial conducted between December 2007 and July 2009 (765,766). The trial included 4,008 patients, aged 18-65 yr, who were obese (BMI, 30-45 kg/m^2) or overweight (27-29.9 kg/m^2) and had

presence of an obesity-related comorbid risk factor. Patients were randomly assigned to receive lorcaserin HCl 10 mg twice daily (BID), once daily (QD), or placebo; all patients received diet and exercise counseling. The primary endpoints were the same as for other lorcaserin trials. Patients treated with lorcaserin 10 mg BID lost 5.8 kg compared with 4.7 kg and 2.9 kg in the patients receiving lorcaserin 10 mg QD or placebo, respectively. Significantly more patients achieved ≥5% total weight loss goal in the lorcaserin BID (47.2%) and lorcaserin QD (40.2%) than in the placebo group (25.0%). The rates of achieving 10% total weight loss among three groups were 22.6%, 17.4% and 9.7%, respectively. Patients taking lorcaserin BID lost more body fat than did patients taking placebo (-9.9% vs. -4.6%, respectively, P<0.01). Men lost more total weight in the lorcaserin BID cohort (-6.0 kg) that in the lorcaserin QD cohort (-5.6 kg), and whites lost more weight than blacks or Hispanics. Dropouts due to adverse effects occurred more frequently in the lorcaserin BID and QD groups (7.2% and 6.2%, respectively) than in the placebo group (4.6%).

When analyzed using a modified intent-to-treat (MITT) strategy, last observation carried forward (LOCF), which included all patients who took at least one dose of study drug and had at least one post-baseline body weight record, minor, not statistically significant changes in LDL-C in the lorcaserin BID group relative to placebo were observed (765,766). As stipulated in the prespecified analysis plan (Hochberg) to adjust for multiplicity, statistical testing stopped when the change in LDL-C did not differ between placebo and lorcaserin BID. According to this testing scheme the other lipid endpoints were not formally tested, although, where reported, *post hoc* analyses demonstrated significant changes in HDL-C and TG between lorcaserin and placebo. ApoB levels were significantly lower in the lorcaserin BID, but neither lorcaserin dose significantly affected ApoA-1 levels.

A per-protocol population was also analyzed and included patients who completed 52-week of study. Overall changes in lipids observed in the per-protocol population were similar to those in the MITT population. Small, not statistically significant changes in total and LDL-C in either lorcaserin dose compared to placebo was observed. However greater decreases in TG (-9.1% vs. -3.2%; P=0.001) and ApoB (-3.4% vs. 1.7%; P<0.0001) and a greater increase in HDL-C (5.9% vs. 3.2%; P<0.001) were observed in lorcaserin BID vs. placebo, respectively.

The BLOOM-DM trial was a randomized, placebo-controlled trial that enrolled 604 patients aged 18-65 years with a BMI 27-45 kg/m^2 and with T2DM (767). Patients were treated with metformin, a sulfonylurea or both medications and had a HbA_{1c} level of 7-10%. Patients were randomized to placebo or to lorcaserin HCl 10 mg once daily (QD) or twice daily (BID) for 1 year; all patients received diet and exercise counseling. The primary endpoints were the same as for BLOOM, and secondary endpoints included changes from baseline in glycemic control, fasting plasma glucose, fasting insulin, HOMA-IR, lipids (TC, LDL-C, HDL-C, TG), physical measures (WC, BMI, systolic blood pressure, diastolic blood pressure), and quality of life, as assessed by the Impact of Weight on Quality of Life-LITE questionnaire. More patients assigned to lorcaserin BID (66%) and lorcaserin QD (79%) completed the study compared to placebo (62%). Of those who completed the study, weight loss was -5.6 kg in the lorcaserin BID, -5.9 kg in the lorcaserin QD

and -1.9 kg in the placebo group. Mean HbA_{1c} decreased significantly in the lorcaserin groups as compared to placebo at all time points, as did fasting plasma glucose. Significantly more patients in the lorcaserin BID (50.2%) and lorcaserin QD (52.2%) achieved HbA_{1c} ≤7% goal versus only 26.3% of patients in the group. Insulin resistance, as indicated by HOMA-IR, was reduced significantly in the lorcaserin BID compared to the placebo group. Symptomatic hypoglycemia was more frequent in the lorcaserin groups (7.4% and 10.5% for BID and QD groups respectively) than in the placebo group (6.3%). At week 52, one patient in the placebo group (0.5%), two (2.5%; P=0.187) in the lorcaserin QD group, and six (2.9%; P=0.122) in the lorcaserin BID group had echocardiographic FDA-defined valvulopathy that was not present at baseline, though findings need to be interpreted with cautions due to small sample size.

Similar to the BLOSSOM trial, overall changes in cholesterol and TG were minimal in all treatment groups, and the differences between treatment groups did not reach statistical significance. According to the prespecified statistical testing conditions, the changes in the total, LDL, and HDL-C were not formally tested since the difference between lorcaserin BID and placebo change in TG was not significant.

Lorcaserin- Safety and Side Effects:

Initially, the FDA Advisory Committee raised numerous safety concerns regarding lorcaserin (768). The committee expressed concerns that the drug was the “chemical cousin” of fenfluramine and dexfenfluramine, raising uncertainty over lorcaserin’s cardiac valvulopathy risk. In addition, there was some evidence that lorcaserin can cause fibroadenomas and adenocarcinomas in animal models. Arena Pharmaceuticals addressed these concerns and ultimately the Advisory Committee members were largely satisfied with the results of additional studies provided.

Overall, lorcaserin is well tolerated. The most common adverse events in clinical trials were upper respiratory infections, headache, dizziness, nasopharyngitis, back pain and nausea. These symptoms were mild and generally resolved quickly. In these trials treatment-emerged adverse events that resulted in treatment withdrawal occurred in 8.6% of lorcaserin recipients and 6.7% of placebo recipients (769). The incidence of depression, depressive symptoms or depressed mood (2.5%) as well as incidence of suicidal thoughts according to one item on the Beck Depression Inventory II (1.3) was relatively low.

Cardiac valvulopathy (mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation) has been evaluated across several lorcaserin studies. The original drug application for lorcaserin showed a higher prevalence of FDA-defined valvulopathy in study subjects. In the BLOOM trial, at year 1, valvulopathy had developed in 2.7% of patients in lorcaserin and 2.3% patients in placebo group (P=0.07), with lorcaserin RR=1.1 (95% CI 0.69 to 1.85). Rates of valvulopathy at year 2 were 2.6% vs. 2.7% for lorcaserin and placebo respectively. In the FDA briefing report, using combined data on all patients who were exposed to lorcaserin or to the placebo in these three trials, no statistically significant difference in

echocardiographic findings for aortic insufficiency or mitral regurgitation has been noted in the lorcaserin vs. placebo group. FDA has not recommended routine echocardiography for prescription of the medication.

Another potential side effect of lorcaserin is the serotonin syndrome, and 1.0% of lorcaserin and placebo recipients reported various symptoms including chills, tremor, confusional state, disorientation, and hyperhidrosis - all of which may be of serotonergic etiology. It was reported that only two lorcaserin recipients had signs and symptoms consistent with serotonergic excess (770,771). Although the incidence of serotonin syndrome is very low, an association between lorcaserin and serotonin syndrome cannot be excluded on the basis of these data. Further, lorcaserin should be used with extreme caution in combination with other drugs that affect serotonin neurotransmitter systems such as triptans, serotonin reuptake inhibitors, monoamine oxidase inhibitors, selective serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants. Longer term studies to further validate such potential risks are planned.

PHENTERMINE/TOPIRAMATE (QSYMIA)

Qsymia, formerly known as Qnexa, was approved by the FDA in July 2012 as an addition to a reduced-calorie diet and exercise for adults with an elevated BMI ≥30 kg/m^2 (i.e. obesity) or BMI ≥27 kg/m^2 (i.e. overweight) with the presence of at least one obesity-related comorbidity. Qsymia is a once-daily capsule combining 2 separate drugs with different pharmacokinetics – immediate release phentermine and controlled-release (CR) topiramate. Qsymia is available in following doses: 1) starting - PHEN/TPM 3.75/23 mg; 2) recommended - PHEN/TPM 7.5/46 mg; 3) titration - PHEN/TPM 11.25/69 mg; 4) top - PHEN/TPM 15/92 mg.

Phentermine is an amphetamine-like drug that acts like an appetite-suppressant and promotes weight loss by activation of the sympathetic nervous system and release of noradrenaline from presynaptic vesicles in the lateral hypothalamus. This increase in noradrenaline results in the simulation of beta-2 adrenergic receptors and a resultant suppression of appetite (772,773). Furthermore, it has been suggested that the weight loss effect might be due to increase in resting energy expenditure. Although chemically related to amphetamine, phentermine does not have its addictive potential. Topiramate was originally approved by the FDA in the mid-1990 as an anticonvulsant for the treatment of refractory seizures (epilepsy). It also can be used for prevention of migraine headaches. Later, it was discovered that the agent resulted in diminished weight gain, often seen with antidepressant treatment (751). The exact mechanism for weight loss remains unclear, however, it has been suggested that topiramate's activation of gamma-aminobutyric acid (GABA) receptors might act as an appetite suppressant and thus decrease night time and deprivation-induced feeding (774). Topiramate might also increase levels of hypothalamic corticotropic-releasing hormone, which likely have catabolic effects (775). Further, topiramate might decrease energy storage and usage efficiency and therefore increase energy expenditure (776).

Phentermine/Topiramate: Clinical Trials- Effect on Lipids:

The effectiveness and safety of Qsymia has been evaluated in several Phase III trials: EQUIP (controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial), CONQUER (effects of low-dose, controlled-release phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese Adults) and the SEQUEL extension of the CONQUER (two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults: a randomized, placebo-controlled, phase 3 extension study) (Table 14).

Table 14. Phentermine/Topiramate Phase III Clinical Trials

	EQUIP	**CONQUER**	**SEQUEL**
Study-group assignment	PHEN/TPM 3.75/23 mg (n=241) PHEN/TPM 15/92 mg (n=512) Placebo (n=514)	PHEN/TPM 7.5/46 mg (n=498) PHEN/TPM 15/92 mg (n=995) Placebo (n=994)	PHEN/TPM 7.5/46 mg (n=153) PHEN/TPM 15/92 mg (n=295) Placebo (n=227)
Age at baseline (yr)	43.0/43.0/41.9	51.1/51.0/51.2	52.2/51.2/52.7
Weight at baseline (kg)	118.5/115.2/115.8	102.6/103.0/103.3	102.2/101.9/101.1
BMI at baseline (kg/m^2)	42.6/41.9/42.0	36.2/36.6/36.7	36.1/36.2/36.0
Duration of study	56 week	56 week	52 week (extension of COQUER)
Primary endpoints	Mean percentage change in BW; proportion of patients achieving ≥5% BW reduction.		
Secondary endpoints	Weight loss; proportion of patients achieving ≥10% BW reduction; change in included changes in BMI, blood pressure, lipids, glycemic measurements (fasting glucose, HbA_{1c}, fasting insulin), biomarkers, concomitant medications for weight-related comorbidities, and rate of progression to diabetes among subjects without diabetes at baseline.		
Patients completing the study (%)	PHEN/TPM 3.75/23: 138 (57.3%) PHEN/TPM 15/92: 301 (58.8%) Placebo: 241 (46.9%)	PHEN/TPM 7.5/46: 334 (69.1%) PHEN/TPM 15/92: 635 (63.8%) Placebo: 565 (56.8%)	PHEN/TPM 7.5/46: 127 (82.5%) PHEN/TPM 15/92: 245 (83.1%) Placebo: 196 (86.3%)

Patients achieving ≥5% weight loss (%)	PHEN/TPM 3.75/23: 44.9% PHEN/TPM 15/92: 66.7% Placebo: 17.3%	PHEN/TPM 7.5/46: 62% PHEN/TPM 15/92: 70% Placebo: 21%	PHEN/TPM 7.5/46: 75.2% PHEN/TPM 15/92: 79.3% Placebo: 30.0%
Patients achieving ≥10% weight loss (%)	PHEN/TPM 3.75/23: 18.8% PHEN/TPM 15/92: 47.2% Placebo: 7.4%	PHEN/TPM 7.5/46: 37% PHEN/TPM 15/92: 48% Placebo: 7%	PHEN/TPM 7.5/46: 53.9% PHEN/TPM 15/92: 50.3% Placebo: 11.5%
Weight loss (%)	PHEN/TPM 3.75/23: -5.1% PHEN/TPM 15/92: -10.9% Placebo: -1.6%	PHEN/TPM 7.5/46: -7.8% PHEN/TPM 15/92: -9.8% Placebo: -1.2%	PHEN/TPM 7.5/46: -9.3% PHEN/TPM 15/92: -10.5% Placebo: -1.8%
Lipids, % change from baseline (PHEN/TPM 15/92 vs. placebo)	TC: -6.0 vs. -3.5; P=0.0014 LDL-C: -8.4 vs. -5.5; P=0.0157 HDL-C: 3.5 vs. 0.0; P=0.005 TG: -5.2 vs. 9.1; P<0.0001 TC/HDL-C: -0.35 vs. -0.09; P<0.0001	TC: -6.3 vs. -3.3; P<0.0001 LDL-C: -6.9 vs. -4.1; P=0.0069 HDL-C: 6.8 vs. 1.2; P<0.0001 TG: -10.6 vs. 4.7; P<0.0001	LDL-C: -5.6 vs. -10.7; P<0.01 HDL-C: 11.9 vs. 4.7; P<0.0001 Non-HDL-C: -9.3 vs. -9.7; NS TG: -13.7 vs. 0.4; P<0.0001

NS, not significant

The EQUIP TRIAL was a double-blind, parallel-group design study of 91 US sites involving 1,267 patients (aged 18-70 years), with class II and III obesity (BMI ≥ 35 kg/m^2), fasting blood glucose <110 mg/dL, TG ≤200 mg/dL and blood pressure ≤ 140/90 mmHg (patients could be on lipid lowering and hypertensive medication) for a total treatment duration of 56 weeks (777). Patients were randomized to placebo (n=514), PHEN/TPM CR 3.75/23 mg (n=214) or PHEN/TPM CR 15/92 mg (n=512), added to a standardized life-style program. Similar to the CONQUER trial, the primary end points were percent of weight loss and proportions of patients achieving 5% weight loss. The secondary end points included improvements in any of the complications of obesity, such as waist circumference, systolic and diastolic blood pressure, fasting glucose and lipid measures. At the end of 56 weeks, patients in the placebo, PHEN/TPM CR 3.75/23 mg and PHEN/TPM CR 15/92 mg groups lost 1.6%, 5.1% and 10.9%, respectively, of their baseline body weight (P<0.001). Percentages of patients who lost >5% of body weight were 17.3% on placebo, 44.9% on PHEN/TPM CR 3.75/23 mg and 66.7% on PHEN/TPM CR

15/92 mg groups, respectively. The PHEN/TPM CR 15/92 mg group had significantly greater mean changes, relative to placebo, in waist circumference, systolic and diastolic blood pressure, TG, TC, LDL-C and HDL-C. The PHEN/TPM CR 3.75/23 mg group had numerically, but not always statistically significant changes relative to placebo, in all these variables. Notably, in both EQUIP and CONQUER trials more patients discontinued treatment in the placebo group compared to the PHEN/TPM CR groups. This may be due in part to greater weight loss efficacy in the treatment groups and the patients therefore encouraged to continue their treatment.

Secondary end point analysis revealed that the PHEN/TPM CR 15/92 mg group had significantly greater mean changes, compared to placebo, in TC (-6.0% vs. -3.5%; P=0.0014), LDL-C (-8.4% vs. -5.5%; P=0.0157), HDL-C (3.5% vs. 0%; P=0.0005), TG (-5.2% vs. 9.1%; P<0.0001), and TC/HDL-C ratio (-0.35% vs. -0.09%; P<0.0001). In contrast, the PHEN/TPM CR 3.75/23 mg group had numerically, but not always statistically significant, greater mean changes compared with placebo, in all these lipid variables.

The CONQUER trial was a double-blind, placebo-controlled phase III trial that randomized 2,487 obese patients with a BMI of 27-45 kg/m^2 and two or more comorbidities (hypertension, dyslipidemia, diabetes or prediabetes, or abdominal obesity) to either placebo, once-daily phentermine 7.5 mg plus topiramate 46 mg, or once-daily phentermine 15 mg plus topiramate 92 mg (778). Primary endpoints included the percentage of patients who achieved at least 5% weight loss and the percentage change in body weight. Secondary outcomes were weight loss, proportion of patients achieving at least 10% weight loss, and change in waist circumference. Patients were divided in a 2:1:2 ratio: placebo (n=994), PHEN/TPM CR 7.5/46 mg (n=498), and PHEN/TPM CR 15/92 mg (n=995).

At the completion of 56 weeks of therapy, the placebo-subtracted weight loss was significantly greater in patients taking mid-dose and high-dose PHEN/TPM, with change of body weight of -8.1 kg (P<0.001) and -10.2 kg (P<0.001) for PHEN/TPM CR 7.5/46 mg and PHEN/TPM CR 15/92 mg, respectively, compared with -1.4 kg for patients receiving placebo. A total of 303 (62%) patients taking PHEN/TPM CR 7.5/46 mg and 687 (70%) patients taking PHEN/TPM CR 15/92 mg achieved at least 5% weight loss compared with 204 (21%) patients receiving placebo. A similar pattern was observed with 10% or more weight loss threshold: 37% and 48% of patients achieved >10% goal in the two groups receiving PHEN/TPM CR compared to 7% for patients receiving placebo.

Significant improvements in blood lipids were observed at the completion of 56 weeks of therapy. Compared with the placebo, mid-dose PHEN/TPM CR 7.5/46 mg significantly reduced TC by -4.9% and TG by -8.6% and increased HDL-C by 5.2%. Greater improvements in blood lipids were seen in patients taking PHEN/TPM CR full dose: reduced TC -6.3%, LDL-C -6.9%, TG -10.6%, and increased HDL-C 6.8%.

The SEQUEL trial was a 52-week extension of the CONQUER trial, investigated the long-term efficacy and safety of two doses of PHEN/TPM CR and lifestyle intervention (total treatment

duration of 108 week) (779). Participants (n=676) continued with the original treatment to which they were randomly assigned during CONQUER. Out of 93 CONQUER sites, 36 sites were selected for the extension study on the basis of their high initial enrollment and rates of retention. At the end of 108 weeks, the percentage changes in body weight from baseline were -1.8%, -9.3%, and -10.5% for placebo, PHEN/TPM CR 7.5/46 mg, and PHEN/TPM CR 15/92 mg, respectively. Further, 10% weight loss was achieved by >50% of PHEN/TPM CR-treated patients, while only <12% subjects receiving placebo met this goal. Discontinuation rates during the extension study were similar between placebo and PHEN/TPM CR-treated patients. The completion rate was about 84%.

Treatment with PHEN/TPM CR 7.5/46 mg and PHEN/TPM CR 15/92 mg resulted to substantially greater reductions in TG (-12.5% and -13.7% vs. 0.4%) and greater increases in HDL-C (7.3% and 11.9% vs. 4.7%) than did placebo. This improvements in TG and HDL-C occurred despite the fact that the placebo group had a noticeably greater net increase in the number of lipid-lowering medications used compared with the PHEN/TPM CR groups. More subjects receiving PHEN/TPM CR had a decrease in lipid-lowering medications than did subjects receiving placebo: 3.1%, 5.9%, and 5.8% for the placebo, 7.5/46, and 15/92 groups, respectively. Conversely, 20.3% of placebo-treated subjects increased lipid-lowering medication use compared with 11.1% in the 7.5/46 group and 10.5% in the 15/92 group. Although LDL-C decreased in all treatment arms, the greatest reduction was seen in the placebo group (-4.6%, -5.6% and -10.7% for the 7.5/46, 15/92 and placebo groups, respectively). Decrease in non-HDL-C was similar in all groups.

Phentermine/Topiramate- Safety and Side Effects:

Vivus, Inc. submitted an initial NDA for Qnexa to the FDA in December 2009, which was denied. Based on the results of Phase III clinical trials, the FDA Advisory Committee largely agreed that the phentermine/topiramate combination resulted in greater weight loss than the use of either drug by itself, and that this weight loss was accompanied by improvements in related comorbidities. However, most of the committee members expressed concerns about potential risks associated with use of antiobesity drugs, especially Qnexa. There were five categories of safety concerns related to Qnexa: psychiatric-related adverse events, cognitive-related adverse events, metabolic acidosis, cardiovascular risks and the teratogenic potential of topiramate when used with phentermine (768). In October 2011, Vivus resubmitted the Qnexa NDA to the FDA, which included additional information such as second-year results from an extension study, a proposed Risk Evaluation and Mitigation Strategy (REMS), as well as proposed labeling including a contraindication for women of reproductive age. Despite concerns about some aspect of the risk mitigation program, the Advisory Committee overwhelmingly voted to recommend FDA approval of phentermine/topiramate combination under its new trade name, Qsymia in 2012.

In general, PHEN/TPM was well tolerated in phase III clinical trials. The most common side effects of PHEN/TPM CR reported in both EQUIP and CONQUER trials were dry mouth,

paresthesia, constipation, insomnia, dizziness and dysgeusia. Dose-related trends in the incident rate of side effects were noted – the rates were generally greater at higher doses of the medication. Psychiatric and cognitive adverse events were observed mainly during the early phase of treatment, and they were resolved on drug discontinuation. Depressive symptoms were assessed using the Patient Health Questionnaire 9 (PHQ-9), and suicide ideation and behavior were assessed using the clinician-administered Columbia Suicide Severity Rating Scale (C-SSRS). Although the incidence of depression was higher with the full dose than placebo, PHQ-9 analyses showed no differences between the groups. Further, no significant increase in suicide risks was identified. In the CONQUER study, 3 serious adverse events of nephrolithiasis occurred in participants treated with high dose PHEN/TPM (778). Topiramate as a carbonic anhydrase inhibitor can decrease serum concentrations of bicarbonate and potassium, therefore increasing the risk of hypokalemia and nephrolithiasis. Careful monitoring of adverse events is advised when PHEN/TPM is used in persons with mild or worse than mild hepatic or renal function. In addition to blood tests, a regular measurement of resting heart rate is recommended in all patients treated with PHEN/TPM. In all three Phase 3 trials, phentermine significantly increased heart rate compared with placebo. Although the clinical significance of increased heart rate is unknown, the use of Qsymia is not recommended in patients with recent or unstable cardiac or cerebrovascular disease.

Phentermine/topiramate is contraindicated in patients with glaucoma or hyperthyroidism, as well as during pregnancy and during or within 14 days following monoamine oxidase inhibitors (MAOIs) use, or in patients with hypersensitivity or idiosyncrasy to sympathomimetic amines, topiramate, or any of the inactive ingredients in Qsymia (780). Further, the FDA recently classified PHEN/TPM in pregnancy category X because of an increased risk for cleft lip and cleft palate during the first trimester of pregnancy (781). In spite of strict study requirements, there were 15 pregnancies in women exposed to PHEN/TPM in EQUIP and 2 in SEQUEL study. Among these pregnancies, there were 3 spontaneous abortions, 3 elective abortions, and 9 healthy live births, while no congenital malformations were observed. As mentioned above, FDA approved Qsymia, with a Risk Evaluation and Mitigation Strategy (REMS), which provides patients with important safety information including prescriber training and pharmacy certification. Qsymia should be only dispensed through specially certified pharmacies. More information regarding Qsymia indication and contraindication, safety information is available at www.qsymia.com/hcp/.

NALTREXONE/BUPROPION (CONTRAVE)

Naltrexone/Bupropion was approved by the FDA in September 2014 as an addition to a reduced-calorie diet and exercise for adults with an elevated BMI ≥30 kg/m^2 (i.e. obesity) or BMI ≥27 kg/m^2 (i.e. overweight) with the presence of at least one weight-related condition such as hypertension, T2DM, or dyslipidemia. Contrave is a combination of two FDA-approved drugs, naltrexone and bupropion, in an extended-release formulation. Naltrexone is an opioid antagonist with a high affinity for the μ-opioid receptor and is approved to treat alcohol and opiate dependence syndrome. Pharmacological pre-clinical studies implicate the μ-opioid

receptor in eating behavior (782). In animal studies naltrexone administration influences activity of the reward system and hedonic eating behavior. Also it has been shown that naltrexone can antagonize the effects of β-endorphins and thus interrupting the negative feedback loop (783). Bupropion is approved and widely used to treating depression and to aid smoking cessation treatment. Bupropion is an amino-ketone class antidepressant, it inhibits reuptake of the catecholamines dopamine and norepinephrine. Its structure closely resembles that of diethylpropion, an anorexiant and sympathomimetic agent. The exact mechanism of action of naltrexone/bupropion as a weight loss agent remains unclear. It has been suggested that while bupropion stimulates hypothalamic proopiomelanocortin (POMC) neurons that release alphamelanocyte stimulating hormone (α-MSH) and β-endorphin, naltrexone antagonizes the effect of β-endorphins and thereby removing the natural “brake” om POMC cells (782). The combination is available as an extended-release tablets, 8 mg naltrexone HCl /90 mg bupropion HCl.

Naltrexone/Bupropion: Clinical Trials, Effect on Lipids:

The effectiveness and safety of Contrave has been evaluated in several phase III trials: Contrave Obesity Research (COR)-I (784), COR-II (785), Contrave Obesity Research Behavior Modification (COR-BMOD) (786), and Contrave Obesity Research-Diabetes (COR-D) (787) including 4536 overweight or obese participants. (Table 15).

Table 15. Naltrexone/Bupropion Phase III Clinical Trials

	COR-I	**COR-II**	**COR-BMOD**	**COR-DM**
Study-group assignment	NB32 (n=583) NB16 (n=578) Placebo (n=581)	NB32 (n=1001) Placebo (n=495)	NB32 (n=591) Placebo (n=202)	NB32 (n=335) Placebo (n=170)
Age at baseline (yr)	44.4/44.4/43.7	44.3/44.4	45.9/45.6	54.0/53.5
Weight at baseline (kg)	99.7/99.5/99.5	100.3/99.2	100.2/101.9	104.2/105.1
BMI at baseline (kg/m^2)	36.1/36.2/36.2	36.2/36.1	36.3/37.0	36.4/36.4
Duration of study	56 week	56 week	56 week	56 week
Primary endpoints	Mean percentage change in BW; proportion of patients achieving ≥5% BW reduction.			

Secondary endpoints	Weight loss; proportion of patients achieving ≥10%, ≥15% BW reduction; change in cardiometabolic risk factors, patient-reported measures of appetite, control of eating and food craving, depressive symptoms, and weight-related quality of life.			
Patients completing the study (%)	NB32: 296 (50.8%) NB16: 284 (49.1%) Placebo: 290 (49.9%)	NB32: 538 (53.7%) Placebo: 267 (53.9%)	NB32: 342 (57.9%) Placebo: 118 (58.4%)	NB32: 175 (52.2%) Placebo: 100 (58.8%)
Patients achieving ≥5% weight loss (%)	NB32: 48% NB16: 39% Placebo: 16%	NB32: 51% Placebo: 17%	NB32: 66% Placebo: 43%	NB32: 45% Placebo: 19%
Patients achieving ≥10% weight loss (%)	NB32: 25% NB16: 20% Placebo: 7%	NB32: 28% Placebo: 6%	NB32: 42% Placebo: 20%	NB32: 18% Placebo: 6%
Weight loss (%)	NB32: -6.1% NB16: -4.9% Placebo: -1.4%	NB32: -6.4% Placebo: -1.2%	NB32: -9.3% Placebo: -5.1%	NB32: -5.0% Placebo: -1.8%
Lipids, % change from baseline (NB32 vs. placebo)	LDL-C: -2.0 vs. -0.5; NS HDL-C: 8.0 vs. 0.8; P<0.0001 TG: -5.2 vs. 9.1; P<0.0001	LDL-C: -6.2 vs. -2.1; P=0.008 HDL-C: 3.6 vs. -0.9; P<0.001 TG: -9.8 vs. -0.5; P<0.001	LDL-C: 5.4 vs. 8.1; P=0.245 HDL-C: 4.1 vs. 0.9; P<0.001 TG: -16.6 vs. -8.5; P<0.004	LDL-C: -1.4 vs. 0.0; P=0.641 HDL-C: 3.0 vs. -0.3; P<0.001 TG: -11.2 vs. -0.8; P<0.007

NS, not significant

The COR-I trial was a multicenter, double-blind, placebo-controlled phase III trial that enrolled 1,742 obese patients aged 18-65 with a BMI of 30-45 kg/m^2 and uncomplicated obesity or BMI of 27-45 kg/m^2 with dyslipidemia or hypertension. Participants were randomly assigned in a 1:1:1 ration to receive sustained-release naltrexone 32 mg/bupropion 360 mg per day (NB32), sustained-release naltrexone 16 mg/bupropion 360 mg per day (NB16), or matching placebo twice a day, given orally for 56 weeks (784). Co-primary endpoints included the percentage change in body weight and the percentage of patients who achieved at least 5% weight loss. Additional endpoints were proportion of participants with decrease in body weight of 10% or more, and 15% or more, change in cardiometabolic risk factors, patient reported measure of appetite, control of eating and food craving, depressive symptoms, and weight related quality of life. 56 weeks of therapy with naltrexone plus bupropion combined with mild diet and exercise resulted in greater weight loss and improvement in cardiometabolic risk factors compared with placebo. Weight loss was significantly greater in patients assigned to naltrexone 32 mg plus

bupropion (mean change in bodyweight -6.1%) and naltrexone 16 mg plus bupropion (-5.0%) groups than in patients receiving placebo (-1.3%). More patients assigned to naltrexone 32 mg plus bupropion and to naltrexone 16 mg plus bupropion groups achieved a decrease in body weight of 5% or more, 10% or more, and 15% or more than did patients in the placebo group.

Regarding lipids, patients assigned to combination treatment with NB16 and NB32 showed a significant decrease from baseline in TG (-8.0% and -12.7% vs. -3.1%) and significant increase in HDL-C (7.6% and 8.0% vs. 0.8%) compared with patients assigned to placebo. Small, not statistically significant changes in LDL-C in either naltrexone plus bupropion dose compared to placebo was observed.

The COR-II trial was a phase III randomized, parallel-arm, double-blind, placebo-controlled, 56-week study. A total of 1,496 obese (BMI 30-45 kg/m^2) or overweight (BMI 27-45 kg/m^2) patients with dyslipidemia were randomized 2:1 to sustained-release naltrexone 32 mg/bupropion 360 mg per day (NB32) or placebo for up to 56 weeks (785). The co-primary endpoints were percent of weight change and proportions of achieving 5% weight loss at week 28. To evaluate the efficacy and safety of a dose increase in patients with suboptimal response, patients with <5% weight loss were re-randomized (double blind) at visits between week 28 and 44 to continue receiving NB32 or escalate to NB48 (sustained-release naltrexone 48 mg/ bupropion 360 mg per day) for the remainder of the study. Weight loss was significantly greater for NB32 vs. placebo at 28 week (-6.5% vs. -1.9%; P<0.001) and it was maintained with continued treatment in the NB32 group through week 56 (-6.4% vs. -1.2%; P<0.001). Further, more NB32-treated achieved >5% weight loss versus placebo at week 28 (55.6% vs. 17.5%) and week 56 (50.5% vs. 17.1%).

NB32 treatment resulted in improvements in secondary endpoints such as cardiometabolic parameters, blood lipids, fasting insulin and HOMA-IR. Among lipid parameters, a significant reduction in TG and LDL-C and increase in HDL-C was seen in patients assigned to NB32 compared with placebo at week 28. These improvements in TG, LDL and HDL-C were not only maintained, but even more enhanced at week 56.

COR-BMOD trial was a 56-week, multicenter, randomized, double-blind, placebo-controlled trial investigated the efficacy and safety of naltrexone plus bupropion as an adjunct to intensive behavior modification (BMOD) (786). 793 obese (BMI 30-45 kg/m^2) or overweight (BMI 27-45 kg/m^2) patients with dyslipidemia were randomized in a 1:3 ratio to: a) placebo + BMOD (n=202); or b) sustained-release naltrexone 32 mg/bupropion 360 mg per day plus BMOD (i.e. NB32 + BMOD, n=591). Both groups were prescribed energy-reduced diet and participate in 28 group BMOD sessions. Co-primary endpoints included the percentage change in body weight and the proportion of patients who lost ≥5% weight at week 56. At week 56, patients treated with placebo + BMOD lost 5.1 ± 0.6% of their initial weight, compared with a significantly greater 9.3 ± 0.4% who received NB32 + BMOD (MITT/LOCF analysis). When analyzing subjects who completed the protocol, weight losses were 7.3 ± 0.9% with placebo + BMOD (N = 106) and 11.5 ± 0.6% with NB32 + BMOD (N = 301). A third analysis, as randomized LOCF sensitivity,

which included all randomized participants, demonstrated losses of 4.9 ± 0.6 and 7.8 ± 0.4%, for the two groups respectively. Further, significantly more NB32 + BMOD treated patients compared with placebo + BMOD treated participants lost ≥5 and ≥10% of initial weight.

Similar to the COR-I trial, significant reduction in TG (-16.6% vs. -8.5%; P=0.004) and increase in HDL-C (4.1% vs. 0.9%; P<0.001) was seen in NB32 + BMOD treated patients compared with placebo + BMOD treated patients. Small, not statistically significant increases in LDL-C were observed in both treatment arms.

The COR-DM was a 56-week, randomized, double-blind, placebo-controlled study, which assessed the efficacy and safety of naltrexone plus bupropion in overweight/obese individuals with type 2 diabetes with or without background of oral antidiabetes drugs. A total of 505 patients were randomized 2:1 to sustained-release naltrexone 32 mg/bupropion 360 mg per day (NB32) or placebo (787). Co-primary end points were percent weight change and achievement of ≥5% weight loss. Secondary end points included achievement of HbA_{1c} <7%, achievement of weight loss ≥10%, and change in HbA_{1c}, waist circumference, fasting blood glucose, and lipids. In the MITT population, patients treated with NB32 lost significantly more weight than placebo-treated patients (-5.0% vs. -1.8%; P<0.001). Similar results were observed among subjects who completed the study (-5.9% vs. -2.2%; P<0.001). More patients treated with NB32 achieved ≥5% weight loss (44.5% vs. 18.9%; P<0.001) compared with placebo. In addition, patients treated with NB32 exhibited a significant improvement in HbA_{1c} (-0.6% vs. -0.1%; P<0.001).

In addition to improvement in HbA_{1c}, NB32 treatment resulted in significant improvement in TG and HDL-C levels in type 2 diabetic patients. However, no significant differences were observed between the naltrexone plus bupropion and placebo groups for LDL-C levels.

Naltrexone/Bupropion- Safety and Side Effects:

Orexigen Therapeutics, Inc. submitted an initial NDA to the FDA for Contrave in March 2010. However, in February 2011, the FDA failed to approve Contrave due to concerns about its cardiovascular safety profile. The sponsor reapplied for FDA approval in December 2013 based on encouraging results of the interim analysis of the Light study, the Contrave cardiovascular outcomes trial (CVOT). Finally, in September 2014, the FDA approved Contrave as treatment option for chronic weight management in addition to a reduced-calorie diet and physical activity. However, with this marketing permission of Contrave, the FDA is requiring several post-marketing studies including a cardiovascular outcomes trial to evaluate the cardiovascular risk; two efficacy, safety, and clinical pharmacology studies in pediatric patients; a nonclinical (animal) juvenile toxicity study focusing on growth and development as well as behavior, learning and memory; a study investigating effects on cardiac conduction; a study to evaluate the effect of Contrave on cardiac conduction; a clinical trials to evaluate dosing in patients with hepatic or renal insufficiency; and a clinical trial to assess potential drug interactions between Contrave and other drugs (788).

Because of the presence of bupropion, the extended release formulation carries a black box warning to alert health care professionals and patients to the increased risk of suicidal thoughts and behaviors as well as risk of serious neuropsychiatric events that have been reported in individuals taking bupropion for smoking cessation (788). Contrave can cause seizures and must not be used in patients who have seizure disorders. The risk of seizure is dose-related. Contrave should be discontinued and not restarted in patients who experience a seizure while being treated with this agent. Contrave can also raise blood pressure and heart rate and must not be used in patients with uncontrolled high blood pressure. The clinical significance of the increases in blood pressure and heart rate observed with Contrave treatment is unclear, especially for patients with heart-related and cerebrovascular (blood vessel dysfunction impacting the brain) disease, since patients with a history of heart attack or stroke in the previous six months, life-threatening arrhythmias, or congestive heart failure were excluded from the clinical trials. Blood pressure and pulse should be measured prior to starting the drug and should be monitored at regular intervals, particularly among patients with controlled high blood pressure prior to treatment. In general, naltrexone/bupropion was well tolerated in phase III clinical trials. The most common adverse events reported in COR trials were nausea (32.5%), which in most cases was transient for the first few weeks of treatment. Other treatment side effect were constipation (19.2%), headache (17.6%), vomiting (10.7%), dizziness (9.9%), insomnia (9.2%), dry mouth (8.1%), and diarrhea (7.1%) (789).

LIRAGLUTIDE (SAXENDA)

Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue, with a 97% structural homology to endogenous human GLP-1. Like endogenous GLP-1, liraglutide binds and activates the GLP-1 receptor, which is present in several areas of the brain involved in appetite regulation. Endogenous GLP-1 has a short elimination half-life of 1.5-2 min, due to degradation by the ubiquitous endogenous enzymes (DPP-4 and NEP). Unlike native GLP-1, liraglutide is stable against metabolic degradation by both enzymes and has a long half-life of about 13 hours after once a day treatment by subcutaneous injection (790,791). Liraglutide was initially developed for the treatment of type 2 diabetes mellitus and subcutaneous liraglutide (Victoza, Novo Nordisk A/S, Bagsvaerd, Denmark), at doses up to 1.8 mg a day has shown benefits for glycemic control (792). Further, when studies were conducted in a large population, treatment with liraglutide not only improved glycemic control but also produced significant dose-dependent weight loss with limited side effects (793-795). Saxenda (liraglutide [rDNA origin] injection) is prescribed at 3 mg once a day by subcutaneous injection (796).

Liraglutide: Clinical Trials- Effect on Lipids:

The effectiveness and safety of Liraglutide has been evaluated in three phase III trials: SCALE Maintenance (Comparison of Liraglutide Versus Placebo in Weight Loss Maintenance in Obese Subjects) (797), SCALE Diabetes (Liraglutide 3.0 mg for Weight Management in Obese/Overweight Adults with Type 2 Diabetes) (798), and SCALE Obesity and Prediabetes

(Efficacy and safety of liraglutide 3.0 mg for weight management in overweight and obese adults) (799) (Table 16).

Table 16. Liraglutide Phase III Clinical Trials

	SCALE Maintenance	SCALE Obesity and Prediabetes	SCALE Diabetes
Study-group assignment	Liraglutide 3.0 mg (n=212) Placebo (n=210)	Liraglutide 3.0 mg (n=2,487) Placebo (n=1,244)	Liraglutide 3.0 mg (n=423) Liraglutide 1.8 mg (n=211) Placebo (n=212)
Age at baseline (yr)	45.9/46.5	44.5/44.4	55.0/54.9/54.7
Weight at baseline (kg)	100.4/98.7	105.8/105.8	105.7/105.8/106.5
BMI at baseline (kg/m^2)	36.0/35.2	38.2/38.2	37.1/37.0/37.4
Duration of study	56 week	56 week	56 week
Co-primary endpoints	Mean percentage change in fasting BW; the proportion of individuals that maintained the ≥5% reduction in fasting BW achieved during low-calorie diet run-in; the proportion that lost ≥5% of fasting body weight.		
Secondary endpoints	Weight change from randomization to week 56; the proportion of participants that lost >10% of fasting randomization weight; the proportion that maintained >50 and >75% of fasting weight loss during run-in; fasting weight change from randomization to week 68; CVD risk factors and glycemic control parameters.		
Patients completing the study (%)	Liraglutide 3.0 mg: 159 (75%) Placebo: 146 (69.5%)	Liraglutide 3.0 mg: 1,789 (71.9%) placebo: 801 (64.4%)	Liraglutide 3.0 mg: 324 (76.6%) Liraglutide 1.8 mg: 164 (77.7%) Placebo: 140 (66.0%)
Patients achieving ≥5% weight loss (%)	Liraglutide 3.0 mg: 50.5% Placebo: 21.8%	Liraglutide 3.0 mg: 63.2% Placebo: 27.1%	Liraglutide 3.0 mg: 49.9% Liraglutide 1.8 mg: 35.6% Placebo: 13.8%

Patients achieving ≥10% weight loss (%)	Liraglutide 3.0 mg: 26.1% Placebo: 6.3%	Liraglutide 3.0 mg: 33.1% Placebo: 10.6%	Liraglutide 3.0 mg: 23.4% Liraglutide 1.8 mg: 14.4% Placebo: 4.3%
Weight loss (%)	Liraglutide 3.0 mg: -6.2% Placebo: -0.2%	Liraglutide 3.0 mg: -8.4% Placebo: -3.1%	Liraglutide 3.0 mg: -4.7% Liraglutide 1.8 mg: -3.6% Placebo: -2.7%
Lipids, estimated treatment difference (95% CI)	TC: -0.11 (-0.24 to 0.03); P=0.11 LDL-C: -0.09 (-0.20 to 0.02); P=0.11 HDL-C: 0.0 (-0.03 to 0.04); P=0.82 TG: -0.11 (-0.20 to -0.01); P=0.03	N/A	N/A

N/A, not available

The SCALE Maintenance was a 56-week randomized, double-blind, placebo-controlled trial that examined the efficacy of liraglutide for maintaining prior weight loss achieved with a low-calorie diet (797). To qualify for randomization, participants had to lose ≥5% of initial body weight during the low-calorie diet run-in period (4-12 weeks). A total of 422 eligible participants (BMI ≥30 kg/m^2 or ≥27 kg/m^2 with comorbidities were randomly assigned 1:1 to receive once-daily liraglutide 3.0 mg (n=212) or placebo (n=210). Co-primary end points were: 1) mean percentage change in fasting body weight from randomization, 2) the proportion of individuals that maintained the ≥5% reduction in fasting body weight achieved during low-calorie diet run-in, and 3) the proportion that lost ≥5% of fasting body weight after randomization. Secondary efficacy end points were: weight change (kg) from randomization to week 56; the proportion of participants that lost >10% of fasting randomization weight; the proportion that maintained >50 and >75% of fasting weight loss during run-in; and fasting weight change (kg) from randomization to week 68. At week 56, participants in the liraglutide group lost an additional mean 6.2% of randomization weight, compared with a mean loss of 0.2% in the placebo group (P<0.0001). Significantly more liraglutide-treated patients (81.4%) maintained ≥5% weight loss achieved in the low-calorie diet run-in, compared with placebo-treated patients (48.9%). The liraglutide was also superior in the percentage of participants who lost >10% of their randomization weight (26.1 % vs. 6.3%; P<0.0001).

Regarding lipids the net change in all lipid levels (TC, LDL-C, HDL-C, VLDL-C and TG) from randomization to week 56 were of small magnitude. Although the estimated treatment differences for liraglutide-placebo reached statistical significance for TG, the absolute changes from randomization to week 56 were minimal.

The SCALE Diabetes trial investigated the efficacy and safety of liraglutide 3.0 mg, as adjunct to diet and exercise, for weight management in obese and overweight adults with type 2 diabetes mellitus (798). 846 individuals were randomized in a 2:1:1 ratio to liraglutide 3.0 mg, 1.8 mg, or placebo plus diet (500 kcal/day deficit) and exercise for 56 weeks. Liraglutide 3.0 mg and 1.8 mg recipients lost -5.9% and -4.6% of their weight, compared to -2.0% in the placebo group. 49.9% of patients taking liraglutide 3.0 mg, and 35.0% of patients taking liraglutide 1.8 mg achieved at least 5% weight loss compared with 12.7% patients taking placebo. Liraglutide 3.0 mg also achieved superior glycemic control (change in HbA_{1c}, proportion reaching $HbA_{1c} \leq 6.5\%$, and change in FPG) vs. liraglutide 1.8 mg and placebo. No data are currently available regarding the effect of liraglutide on the lipid profile.

The SCALE Obesity and Prediabetes trial investigated the efficacy and safety of liraglutide 3.0 mg, as adjunct to diet and exercise, for weight management in obese and overweight adults without type 2 diabetes mellitus (799). 3,731 individuals were randomized 1:1 to liraglutide 3.0 mg, or placebo plus diet (500 kcal/day deficit) and exercise for 56 weeks. Randomization was stratified by prediabetes status (ADA 2010) and BMI. Patients receiving liraglutide 3.0 mg lost -8.0% of their weight compared to -2.6% receiving placebo ($P<0.0001$). Significantly more patients taking liraglutide 3.0 mg, achieved at least 5% and 10% weight loss when compared with patients taking placebo. Liraglutide 3.0 mg also improved glycaemia, blood pressure and lipids (data not shown). Weight loss independent of pre-treatment prediabetes status and BMI.

Liraglutide- Safety and Side Effects:

Saxenda is manufactured by Novo Nordisk A/S, Bagsvaerd, Denmark and is distributed by Novo Nordisk, Inc. Plainsboro, New Jersey. The sponsor has submitted the NDA to the FDA for Saxenda on December 20, 2013. Liraglutide was approved on December 23, 2014 by the U.S. FDA under the trade name Saxenda as a treatment option for chronic weight management in addition to a reduced-calorie diet and physical activity (800). However, the FDA is requiring the following post-marketing studies including clinical trials to evaluate dosing, safety, and efficacy in pediatric patients; a study to assess potential effects on growth, sexual maturation, and central nervous system development and function in immature rats; an medullary thyroid carcinoma (MTC) case registry of at least 15 years duration to identify any increase in MTC incidence related to Saxenda; and an evaluation of the potential risk of breast cancer with Saxenda in ongoing clinical trials (800). Currently, cardiovascular safety of liraglutide is being investigated in an ongoing cardiovascular outcomes trial (801). Further, the FDA approved Saxenda with a REMS, which consists of a communication plan to inform health care professionals about the serious risks associated with Saxenda.

Serious side effects reported in patients treated with Saxenda include pancreatitis, gallbladder disease, renal impairment, and suicidal thoughts. In the clinical trials, 68% of Saxenda treated patients reported gastrointestinal events, of which the most common was nausea (39%). Most nausea events developed within the first 4 weeks and the percentage of patients reporting nausea declined as treatment continued. Other common side effects included diarrhea,

constipation, vomiting, dyspepsia, abdominal pain, dry mouth, gastritis, gastrointestinal reflux disease, flatulence, eructation and abdominal distention (802,803). The events were mostly transient and of mild or moderate intensity, and the event frequency were dose dependent. Other side effects include a minor (2-3 beats/min) increases in resting heart rate in Saxenda-treated patients. Although the clinical significance of the heart rate elevation is unclear, especially in patients with cardiac and cerebrovascular disease, some preclinical studies reported that GLP-1 agonists have beneficial effect on cardiovascular outcomes (804).

Surgical Treatment of Obesity

As stated above, traditional medical management of obesity, such as lifestyle interventions, behavioral modifications and pharmacological agents usually have modest success rates – only about 5-10% of severely obese patients are able to achieve long-lasting weight reduction. In 1991, the NIH released a Consensus Statement entitled “Gastrointestinal Surgery for Severe Obesity”, which recommended obesity surgery for long-term weight control and specified criteria for patient selection (805). Recently, updated clinical practice guidelines was jointly developed by the American Association of Clinical Endocrinologists, The Obesity Society, and the American Society for Metabolic & Bariatric Surgery for the peri-operative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient (806). According to current guidelines, the following patients should be considered as candidates for bariatric surgery: a) patients with a severe obesity (BMI≥40 kg/m^2) without coexisting medical problems, and for whom bariatric surgery would not be associated with excessive risk; b) patients with moderate obesity (BMI≥35 kg/m^2) and one or more severe obesity-related co-morbidities, including type 2 diabetes, hypertension, hyperlipidemia, obstructive sleep apnea (OSA), obesity-hypoventilation syndrome (OHS), Pickwickian syndrome (a combination of OSA and OHS), nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis, pseudotumor cerebri, gastroesophageal reflux disease, asthma, venous stasis disease, severe urinary incontinence, debilitating arthritis, or considerably impaired quality of life (806). Bariatric surgery should be considered only for well-informed and motivated patients with acceptable risks, and patients should have failed previous attempts at supervised weight reduction programs and demonstrate realistic expectations about long-term outcomes achievable with surgery.

A number of bariatric surgical procedures have been developed for treatment of obesity (807,808), based on the concept that restricting intake and induced malabsorption, or both, will reduce body weight. Currently, there are four types of operations that are commonly offered in the United States: The Roux-en-Y gastric bypass (RYGB), the laparoscopic adjustable gastric band (LAGB), biliopancreatic diversion (BPD) with or without duodenal switch (BPD-DS), and the more recent laparoscopic sleeve gastrectomy (LSG). Each has its own benefits and risks. Some procedures used previously are no longer in use, such as intestinal bypass in which large amount of small intestine was bypassed. The flaw of these operations was that large segments of intestine had neither food nor bilio-pancreatic fluid going through it. In many patients these operations let to a number of complications such as impaired fat absorption, autoimmune diseases, protein malnutrition and these operations are no longer done. The first restrictive

procedure was the horizontal gastroplasty in the 1970s which involves partitioning the stomach into a small upper reservoir so that the patient feels full with a small amount of food. However, the weight loss results were poor and the failure rate high (reoperation rate was 15%), and it was replaced by vertical banded gastroplasty (VBG) in 1980s (809). VBG was one the most popular procedures in the US until 1990s when it was replaced by the combination of restrictive surgery with malabsorption procedure, known as the Roux-en-Y gastric bypass.

ROUX-EN-Y GASTRIC BYPASS (RYGB)

RYGB was first reported by Drs. Mason and Ito in 1960s, and its popularity increased in the 1980s with improvement of techniques into its current form, using a Roux-en-Y limb of intestine. The gastric bypass was based on weight loss observed among patients undergoing partial stomach removal for cancer and ulcers. The procedure involves partition of the upper part of the stomach using surgical staples to create a small pouch (50 ml or less) and then performing a gastrojejunostomy utilizing a Roux limb of jejunum that allow the pouch to empty. The primary mechanism of weight reduction is calorie restriction although malabsorption may also play a role in longer Roux limbs. Laparoscopic RYGB, introduced by Wittgrove in 1994 (810), has currently become the mainstay bariatric procedure worldwide. According to the American Society for Bariatric Surgery and the National Institutes of Health, RYGB is the most frequently performed operation for weight loss in the US, and is considered by many surgeons to be the “gold standard” to which all other surgical procedures are compared. Complications of the RYGB include anastomotic leaks, vomiting caused by narrowing of the stoma due to scar tissue development, and dumping syndrome (an adverse event caused by eating refined sugar)

RYGB- Effect on Lipids:

In general, RYGB surgery tends to result in substantial improvements in cardiometabolic risk factors and circulating lipid levels that are proportional to the magnitude of weight loss (811,812). For example, in patients undergoing laparoscopic RYGB surgery, excess weight loss at one year post-operatively was associated with a 16% decrease in TC, 31% in LDL-C, 63% in TG, 74% in VLDL-C, 60% in total to HDL-C ratio and a 39% increase in HDL-C (813). In a small study in morbidly obese subjects, there was a significant reduction in TG, a significant increase in HDL-C and a reduction of atherogenic small dense LDL with an increase of large buoyant particles (814). A longitudinal analysis performed in 949 patients demonstrated that plasma concentrations of TG, LDL-C and HDL-C were all significantly improved one year after RYGB surgery (815). These improvements in lipid profile were independent of weight loss. A small prospective study reported a significant decrease in levels of ApoB100 (22.9% reduction at 3 months and 32.1% reduction at 6 months) (816). This change in ApoB100/ApoA-1 ratio correlated significantly with the changes in TC, LDL-C and TG levels. In a recent, randomized, parallel group trial, Sovik et al. compared effect of gastric bypass and duodenal switch on cardiovascular risk factors (817). The authors report that 2 years after surgery, total and LDL-C concentration decreased by 9.27 mg/dL (0.24 mmol/L) and 10.0 mg/dL (0.26 mmol/L) after gastric bypass, and 41.3 mg/dL (1.07 mmol/L) and 30.1 mg/dL (0.78 mmol/L) after duodenal

switch respectively. Both surgery groups had significant reduction in mean TG concentrations and significant increase in mean HDL-C concentrations.

LAPAROSCOPIC ADJUSTABLE GASTRIC BAND (LAGB)

LAGB is the most recent variation of the gastric restriction procedures, approved by FDA in 2001 (818). This procedure was introduced to the clinical realm by Dr. Kuzmak, who reported that patients with adjustable silicone bands lost significantly more weight compared with those who had nonadjustable bands (819,820). The procedure involves the placing of an inert inflatable band around the proximal stomach creating a 5-15 ml pouch that offers the opportunity for precise adjustment of the degree of restriction. The LAGB is purely restrictive, and technically a simpler operation than the VGB or RYGB with minimal surgical trauma. Although the gastric band is removable, requiring only a laparoscopic procedure to remove the band, allowing the stomach to return to its normal pre-banded size, adhesions and tissue scars are unavoidable. Complications of LAGB are ulceration, band migration, erosion, slippage, and malfunction, but the recent design and placement technique improvements appear to reduce the complications. A recent longitudinal cohort study of the LAGB patients demonstrated that they achieved and maintained a loss of 47% excess weight to 15 years (821). According to recent data analysis of the bariatric surgery admissions from 2008 to 2012, the use of LAGB, has decreased over the last few years compared with other bariatric surgical procedures such as RYGB or LSG (822).

LAGB- Effect on Lipids:

In regard to changes in lipid profiles after LAGB, while most studies report an improvement of plasma TG and HDL-C, changes in the cholesterol level are reported to vary between the studies. An early study by Busetto et al. investigated the effect of different levels of weight reduction needed to achieve a clinically meaningful effect on lipid levels in morbidly obese patients undergoing adjustable gastric banding surgery. The authors found that a moderate weight loss (10-20% of initial weight) was able to produce the maximal effect on lipid levels, but more pronounced degree of weight reduction did not add additional benefits to the lipid profile (823). Nguyen et al. evaluated weight loss and surgical outcomes of RYGB and LAGB from the Australian prospective surgical databases. Overall improvements in TC, TG and HDL-C after both RYGB and LAGB was reported (824). In an Australian study enrolling 1,176 patients, adjustable gastric band surgery resulted in overall improvement in cardiovascular risk factors including significant decrease in blood pressure, plasma TG and increase in HDL-C levels. However, unexpectedly, there were also significant increases in total and LDL-C levels (825). Dixon and O'Brien reported favorable changes in TG, HDL-C and TC/HDL-C ratio, but no changes in total and LDL-C level in patients with and without diabetes (826,827). Another small prospective, randomized trial in diabetic patients did not find any changes in lipid profile 1-year after LAGB surgery (828). A longitudinal cohort study in diabetic patients reported an improvement in most metabolic outcomes including a significant reduction in TG and increase in HDL-C that was sustained for at least 5 years (829).

BILIOPANCREATIC DIVERSION (BPD) WITH OR WITHOUT DUODENAL SWITCH (BPD-DS)

The BPD (BPD-DS) was first described by Dr. Scopinaro in 1979 in Genoa (830). It is a combination of gastrectomy and intestinal bypass and is one of the most technically demanding bariatric procedures associated with a high rate of perioperative morbidity. The procedure contains a restrictive component, but it is primarily a malabsorptive procedure and results in a substantial weight reduction (up to 80% of excess weight) (831). Although presently it constitutes less than 2% of bariatric surgery procedure worldwide (832), sometimes it is used as an option in specific situations or with noncompliant patients, such those with Prader-Willi syndrome. Complications of the procedure includes anastomotic leak and ulceration (3%-10%), severe protein malnutrition, hypoalbuminemia, fat-soluble vitamin deficiency, anemia, diarrhea, and osteoporosis (831).

BPD-DS- Effect on Lipids:

Regarding improvements in lipid profile after BPD, most studies report a significant improvement in lipid levels, including reduction in cholesterol, TG, ApoB levels and increase in HDL-C. Scopinaro et al. observed in a 10-year follow-up study on subjects with metabolic syndrome, that throughout all the follow-up period, significant improvements in mean body weight as well as in serum TG and TC levels remained unchanged at levels reached at 1 year after BPD (833). In a recent study, Piché et al. investigated the impact of BPD-DS surgery on cardiovascular risk profile in severely obese patients (834). At 1-year after BPD-DS surgery, a marked decrease in body weight (38% loss in initial body weight) was associated with significant reductions in TC, LDL-C, TC/HDL-C ratio, TG and ApoB levels (834). A small prospective study reported an early and significant reduction of TC (32.8%), LDL-C (46.3%), ApoB (37%) and TG (21.3%) after BPD. Significant improvements in lipid profile after BPD surgery were also reported in studies involving patients with T2DM (835-837). Benetti et al. assessed intestinal cholesterol absorption in obese patients undergoing biliopancreatic diversion and adjustable gastric banding surgery. Although the weight loss was similar in both surgical groups, serum TC, LDL-C, non-HDL-C decreased only in the former group (838). The long-term follow-up data available after BPD supports its efficacy as a potential cure for morbid obesity and improvements in related metabolic disorders including changes in the lipid profile (839,840).

LAPAROSCOPIC SLEEVE GASTRECTOMY (LSG)

More recently, the laparoscopic sleeve gastrectomy described by Ren et al. (841) is rapidly gaining popularity as the preferred bariatric approach (842). The LSG, a stand-alone laparoscopic procedure, was initially described as the first-step operation for high-risk morbidly obese patients undergoing BPD-DS. The approach was to perform a safer and simpler procedure to get initial weight loss and then after 12 months, under more optimal healthier condition, complete the BPD-DS to achieve the malabsorption effect. However, it became evident that the LSG in itself provided a substantial and long-lasting weight loss and thus the

second stage of BPD-DS was rarely needed (843). The procedure partitions the stomach along its vertical length by removing its entire fundus and a majority of the body and creating a narrow gastric pouch. This procedure provides significant mechanical restriction with no malabsorption component or dumping, in addition changes in the hormonal and entero-insular axis might also contribute to the efficacy of the procedure. Complications are relatively rare, with a low postoperative mortality rate (1%). The American College of Surgeons - Bariatric Surgery Center Network (ACS-BSCN) recently analyzed retrospectively collected bariatric-specific data and compared the sleeve gastrectomy to the established treatment of obesity: adjustable band (LAGB) and gastric bypass (laparoscopic and open RYGB) (844). LSG was positioned between the LAGB and the RYGB in terms of effectiveness and morbidity for data up to one year.

LSG- Effect on Lipids:

Compared to other bariatric procedures, limited information is available regarding the effect of LSG on lipid profiles since it only recently been recognized as a primary procedure (845). As discussed above, while significant decreases in total and LDL-C levels have been reported after RYGB and BPD surgery, not all patients who had a sleeve procedure have been found to have reduced LDL-C levels (846-849). Hady et al. assessed the impact of laparoscopic gastric banding and laparoscopic sleeve gastrectomy on metabolic parameters in obese patients (850). At 6 months post-surgery, both procedures resulted in a significant reduction of TC, LDL-C, and TG, however there were no significant changes in HDL-C levels (850). A recent study compared medium-term (5 years) impact of LSG with two gastric bypass techniques in 519 morbid obese patients (851). Although LSG resulted in weight reduction that was similar or greater to that from RYGB, LSG was found to be inferior to gastric bypass techniques in terms of lowering blood lipid levels (TC and LDL-C levels) (851). Notably, in a number of recent studies TC was shown to increase after sleeve gastrectomy (847,849,852,853). In general, LSG lead to significant improvements in plasma HDL-C and TG level (847-849). Dogan et al. report that early postoperative changes in LDL and HDL subfraction profile after LSG were accompanied by a significant decrease in HDL-associated enzymes (CETP and LCAT). Another recent study explored early metabolic response following LSG in diabetic obese patients (854). At 1 week after surgery, there was no change in TC, but LDL-C and non-HDL-C increased significantly, and HDL-C decreased significantly (854).

Medical Devices for Treatment of Obesity

GASTRIC BALLOON SYSTEMS

In 2015, the FDA approved two intragastric balloon (IGB) devices (Orbera and Reshape Duo) for use in the USA, though saline-filled IGB have been used outside of the USA since 1997. In the following year, the Obalon Balloon System was approved by the FDA. The IGB systems has been approved for temporary use (up to 6 months) as an adjunct to weight reduction for obese adults with a BMI of 30-40 kg/m^2 and to be used in conjunction with a long-term diet and lifestyle modification program. The mechanism of action is poorly understood; putatively, IGB may act by

partially filling the stomach and reducing gastric volume, delayed gastric emptying, and stimulation of mechanosensitive receptors in the gastric wall. The IGB is placed in the stomach and designed to dwell in the stomach for a maximum of 6 months.

Orbera is one of the widely used IGB device and has been used outside of the USA for over 18 years in more than 80 countries (855). Multiple earlier studies have shown efficacy and satisfactory weight loss with Orbera. A recent pivotal randomized clinical trial showed 10.2% total weight loss at 6 months with Orbera compared to 3.3% in the control group (855).

The Reshape Duo device consists of two balloons that is interconnected by a flexible wire and the dual balloon design aims to enhance gastric space filling and reduce the risk of intestinal migration. In a randomized sham controlled REDUCE pivotal trial, 326 patients (mean BMI 35.4 kg/m^2) who had Reshape Duo IGB for 24 weeks demonstrated EWL of 25.1% vs. 11.3% in the control arm. In addition to weight loss, patients with the Reshape Duo had minor improvements in glycemic and lipid parameters compared to those receiving sham treatment (856).

Obalon was approved by the FDA as the first IGB that does not require endoscopic placement (857). It is swallowed in a capsule form in a provider's office, and once position is confirmed by fluoroscopy, the balloon is inflated with 250 ml of nitrogen-sulfur-hexafluoride gas mixture through a connected catheter. Up to three balloons can be swallowed in the same session or sequentially over a 12-26-week treatment period, after which the balloons are deflated and removed endoscopically. In a pivotal multi-center randomized blinded clinical trial the total body weight loss (TBWL) at 6 months among patients with Obalon was 6.9%, compared to 3.6% in control group (858).

Common adverse effects of IGB include vomiting, abdominal cramps, heartburn, nausea, bloating and gastrointestinal reflex and they usually resolve completely within 4-10 days after placement. Serious adverse events occur relatively rare and include gastroduodenal ulcers, intestinal obstruction caused by balloon deflation and migration, and esophageal/gastric perforation (856). Recently, the FDA warned medical providers about potential risks with fluid filled intragastric balloons (Orbera and ReShape Duo) after receiving reports of acute pancreatitis and spontaneous over-inflation resulting from gas accumulation in the balloon. Neither were listed as potential complications in the initial balloon labeling information.

ELECTRICAL STIMULATION SYSTEMS

The vagus nerve is known to play an essential role in weight regulation through its effects on satiety, metabolism and autonomic control of upper gastrointestinal track. Intermittent vagal blockade (vBloc) therapy was developed as a less invasive alternative method to treat patients with obesity to standard bariatric surgery. A number of RCTs on vBloc therapy have demonstrated a substantial weight loss and improvement in obesity related comorbid conditions such as T2DM and low rate of overall complications (859-861).

The Maestro Rechargeable System (ReShape Lifesciences) was approved by the FDA in 2015 for patients with BMI 40-45 kg/m^2, or BMI 35-40 kg/m^2 with at least one weight related comorbidity. The device, delivers low energy, high frequency, intermittent, electrical impulses to anterior and posterior vagal nerve trunks for a predetermined number of hours each day and its implanted and secured using laparoscopic surgical procedures. In the ReCharge trial, the effect of the vBloc Maestro system on weight loss, obesity-related comorbid conditions and safety was studied in 239 obese patients with BMI 40-45 kg/m^2 (859,861). At 12 months, patients randomized to vBloc group demonstrated a mean 9.2% TBWL compared to 6.0% TBWL in the sham group (P = 0.002) (859). At 24 months, 123 (76%) vBloc participants remained in the trial and demonstrated 8% TBWL (861). Quality of life and eating behavior in the vBloc group was substantially improved. In addition, improvements in cardiovascular, anthropometric and metabolic parameters were observed including statistically significant improvement from baseline in LDL-C, HDL-C, TG and HbA1c. Based on the results of the ReCharge trial data, the vBloc device was approved by the FDA for use in individuals with a BMI of 35-45 kg/m^2.

The most frequently reported adverse events were heartburn, dyspepsia and neuroregulator site pain, other pain, abdominal pain, incision pain, nausea and dysphagia. Most of the adverse events were reported as mild or moderate in severity and typically resolved with little or no intervention. Three serious adverse events of infection, confusion with hallucination and brain tumor were reported and adjudicated by committee to be unrelated to vBloc therapy.

GASTRIC EMPYTING SYSTEMS

Aspirational therapy induces weight loss by direct aspiration of meal after ingestion from the stomach before it passes into small intestine. A percutaneous gastrostomy aspiration tube (the Atube) is placed endoscopically and connected to an external aspiration port that lies flush on the abdominal surface. After the ingestion of each meal, an aspiration device is connected to the port to perform flushing with water followed by aspiration of ~30% of ingested meal. Food particles must be 5 mm or less in diameter, thus patients must take extra time to thorough chewing to ensure food will go through the 6 mm diameter Atube.

The AspireAssist (Aspire Bariatrics, USA) was approved by the FDA in 2016 after PATHWAY pivotal trial (862) for patients aged 22 years and older, with a BMI 35-55 kg/m^2, who have failed to achieve and maintain weight through non-surgical weight-loss therapy. In the PATHWAY trial, 207 participants were randomized in a 2:1 ration to 52 weeks of treatment with AspireAssist plus lifestyle vs. lifestyle therapy alone. At 1 year, patients with AspireAssist showed greater TWBL compared to patients only receiving lifestyle therapy (12.1% vs. 3.6% mean TBWL, respectively) (862). Early studies reported promising results, with the AspireAssist yielding a mean TBWL of 15.2–18.6%. These results led to FDA approval of the device in June 2016 for use in adults (>22 years old) with a BMI between 35–55 kg/m^2 who have not responded to nonsurgical weight loss therapy. The FDA has indicated that AspireAssist is intended for long-term use in conjunction with lifestyle therapy and continuous medical monitoring.

Most frequently reported adverse events include risks associated with placement of conventional gastrostomy tubes, including post-operative abdominal pain, nausea, vomiting, peristomal granulation tissue, and peristomal irritation.

ENDOSCOPIC ENDOLUMINAL BYPASS LINERS

The duodenal-jejunal bypass liner (GI Dynamics, USA), EndoBarrier mimics the intestinal bypass component of RYGB and duodenal-jejunal exclusion surgery. The liner consists of 60 cm long impermeable fluoropolymer sleeve with a nitinol anchor that is endoscopically delivered into the duodenum. The anchor in placed in the duodenal bulb and liner is stretched out through the duodenum and upper jejunum and therefore preventing absorption of nutrients from proximal part of intestine.

Efficacy and safety of EndoBarrier was evaluated in a recent multicenter RCT, which enrolled 77 patients with obesity and T2DM. After 6 months of therapy, patients with EndoBarrier showed significantly more weight loss than control group (mean TBWL 10.0% vs. 4.7%, $P<0.05$) (863). In addition, HbA1c levels decreased significantly compared to control (7.0% vs. 7.9%, $P<0.05$). Marked improvement of T2DM was also observed. However, after removal of the device, weight regain was observed and HbA1c levels increased and at 12 months, the changes in weight and HbA1c levels were no longer statistically different between two groups. Similar results were found in the FDA pivotal ENDO trial – mean change of HbA1c at 12 months 0.8% and mean TBWL was 5.6% compared with sham control (864). In 2016, GI Dynamics announced the final results from the ENDO trial stating that the trial ended early due to a higher-than-normal incidence of liver abscess. EndoBarrier obtained a CE marking to allow use in the European Union, but did not receive FDA approval.

In initial RCT, 76.3% of patients had at least one adverse event vs. 59% in the control group. Common adverse events consisted mainly of minor GI complaints, including abdominal pain or discomfort. In addition, complaints of nausea and vomiting occurred in 23.7% of patients. More serious devise related adverse events include upper GI bleeding, pancreatitis, sleeve migration and/or occlusion, and liver abscesses (865).

SUMMARY

Obesity is a chronic medical condition and has continued to accelerate at an unprecedented rate in the United States and Worldwide. Treatment of obesity is a difficult and complex process and limited effective obesity management systems are in place in national healthcare services around the world. Lifestyle modifications remain the cornerstone of weight management; a pharmacologic treatment is considered when the behavioral approach is not sufficient. Four drugs, lorcaserin (Belviq), phentermine/topiramate (Qsymia), naltrexone/bupropion (Contrave) and liraglutide (Saxenda) have been recently approved by FDA for the treatment of obesity. Although these drugs appear safe, post-marketing long-term studies are ongoing to evaluate their cardiovascular safety. For patients with severe obesity and who meet specific indications,

bariatric surgery can be considered. A range of medical devices for the treatment of obesity, many of which are placed endoscopically, has been recently introduced to bridge the gap between pharmacotherapy and disruptive bariatric surgery. In general, both obesity drugs and bariatric surgery produce favorable effect on plasma lipid levels, however the lipid lowering effect may vary between the treatment regimens as well as between the bariatric procedures.

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