



The Effect of Inflammation and Insulin Resistance on Lipid and Lipoprotein Responsiveness to Dietary Intervention

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ABSTRACT

Lipids and lipoproteins are major targets for cardiovascular disease (CVD) prevention. Findings from a limited number of clinical trials suggest diet-induced atherogenic lipoprotein lowering can be altered in the presence of chronic low-grade inflammation or insulin resistance. This review summarizes results from randomized controlled trials that have examined diet-induced changes in lipids/lipoproteins by inflammatory or insulin sensitivity status. In addition, mechanisms to explain these clinical observations are explored. Post hoc analyses of data from a limited number of randomized controlled trials suggest attenuation of diet-induced lipid/lipoprotein lowering in individuals with inflammation and/or insulin resistance. These findings are supported by experimental studies showing that inflammatory stimuli and hyperinsulinemia alter genes involved in endogenous cholesterol synthesis and cholesterol uptake, reduce cholesterol efflux, and increase fatty acid biosynthesis. Further a priori defined research is required to better characterize how chronic low-grade inflammation and insulin resistance modulate lipid and lipoprotein responsiveness to guide CVD risk reduction in individuals presenting with these phenotypes. *Curr Dev Nutr* 2020;4:nzaa160.

Keywords: inflammation, cholesterol, insulin resistance, diet, proprotein convertase subtilisin/kexin type 9 (PCSK9), C-reactive protein (CRP)

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Abbreviations used: ABC, ATP-binding cassette transporter; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; HNF1 α , hepatocyte nuclear factor-1 α ; hs-CRP, high-sensitivity C-reactive protein; LDL-R, LDL-receptor; LXR, liver-X receptor; p38MAPK, p38 mitogen-activated protein kinase; PCSK9, proprotein convertase subtilisin/kexin type 9; SAA, serum amyloid A; SCD1, stearoyl CoA desaturase 1; SHP, small heterodimer partner; SOCS3, suppressor of cytokine signaling-3; SR-B1, scavenger receptor class B type 1; SREBP, sterol regulatory element binding protein; Step I/II, National Cholesterol Education Program Step I/II (diet); THP-1, human monocytic cell line.

Introduction

Elevated LDL cholesterol is an established causal risk factor for cardiovascular disease (CVD) (1), and reducing LDL cholesterol remains the primary target for CVD prevention (2). First-line intervention for the management of lipids and lipoproteins in primary and secondary prevention of atherosclerotic CVD is a healthy dietary pattern (2). Healthy dietary patterns emphasize intake of vegetables, fruits, whole grains, legumes, nuts, fat-free or low-fat dairy, vegetable or lean animal protein, and nontropical oils; and limit intake of added sugars, sodium, and processed meats (2). This is based on a substantial body of concordant evidence showing that a healthy dietary pattern reduces CVD risk (3–5), in part by improving lipids and lipoproteins. However, published secondary analyses of data from randomized controlled trials of dietary interventions to lower atherogenic cholesterol have shown diminished lipid/lipoprotein lowering in individuals with inflammation or insulin resistance (6–17).

Subclinical low-grade chronic inflammation characterized by high-sensitivity C-reactive protein (hs-CRP) >2 mg/L is an established atherosclerotic CVD risk enhancer (2), and data from primary and secondary CVD prevention trials suggest $\sim 50\%$ of patients have an hs-CRP concentration >2 mg/L, and 35% have an hs-CRP concentration >3 mg/L (18). Chronic inflammation is causally associated with the development of CVD (19), and a large secondary prevention trial of patients with previous myocardial infarction and hs-CRP >2 mg/L showed that reducing inflammation with anticytokine therapy targeting the IL-1 β pathway reduced the incidence of CVD in the absence of changes in lipids/lipoproteins (20). In addition to established mechanisms by which inflammation has been implicated in the etiology of CVD, observations from dietary studies suggest that inflammation can modulate lipid and lipoprotein responsiveness to dietary intervention (6–14).

Likewise, insulin resistance can also diminish diet-induced lipid and lipoprotein lowering. Given the increasing prevalence of prediabetes

and type 2 diabetes in the United States (21), conditions that are characterized by reduced insulin sensitivity, further exploration of these observations is needed to understand the basis for blunted diet responsiveness to assist in the optimization of dietary guidance. In addition, prediabetes and type 2 diabetes confer greater CVD risk (22) and therefore, lipid and lipoprotein lowering is a target of CVD risk reduction strategies for these individuals (2). Thus, the aim of this narrative review is to describe the lipid and lipoprotein modifications observed in response to dietary interventions by the presence of inflammation or insulin resistance. In addition, potential mechanisms to explain how inflammation and insulin resistance might modify lipid metabolism and therefore the response to dietary interventions will be described.

Lipid and Lipoprotein Responsiveness to Dietary Interventions in the Presence of Systemic Inflammation

We used nonsystematic search strategies to identify clinical trials that measured lipids and lipoproteins in response to a dietary intervention and reported results by inflammatory status. Nine clinical trials were identified (Table 1). These trials show that individuals with less systemic inflammation at baseline, as measured by hs-CRP, have greater and more favorable lipid and lipoprotein responses to blood cholesterol-lowering dietary interventions than those with greater inflammation (6–14). These differential lipid/lipoprotein responses by inflammatory status have been observed in the context of a variety of diets lower in saturated fat, including the Dietary Approaches to Stop Hypertension (DASH) diet and the National Cholesterol Education Program Step I (Step I) diet. In 2 randomized controlled feeding trials significant reductions in total cholesterol, LDL cholesterol, and HDL cholesterol were observed with DASH diets compared with average American control diets (6, 7). In addition, there were no changes in hs-CRP with the DASH or control diets. However, in individuals with a baseline hs-CRP less than the median (<2.37 mg/L) a substantial and clinically significant reduction in total cholesterol (−19 mg/dL; 9.8%; $P < 0.001$) and LDL cholesterol (−15 mg/dL; 11.8%; $P < 0.001$) was observed in response to the DASH diet compared with the control diet (6). This benefit was not observed in subjects with an hs-CRP concentration above the median at baseline, in whom no change was observed in LDL cholesterol (−4 mg/dL; 3%; $P > 0.10$) or total cholesterol (−6 mg/dL; 3%; $P > 0.10$) after the DASH diet compared with the control diet. Similarly, Rousell and colleagues (7) observed greater total cholesterol (−28 mg/dL compared with −8 mg/dL) and LDL cholesterol (−18 mg/dL compared with −9 mg/dL) lowering in response to the DASH diet in subjects with an hs-CRP <1 mg/L compared with those with a higher hs-CRP (≥ 1 mg/L).

Differential lipid/lipoprotein responsiveness by inflammatory status has also been observed in a number of other trials where saturated fat was replaced by other macronutrients. In subjects with hypercholesterolemia and lower hs-CRP concentrations (<2 mg/L) a trend towards greater LDL cholesterol lowering was observed with diets high in α -linolenic acid or linoleic acid relative to subjects with higher hs-CRP concentrations (>2 mg/L; $P = 0.068$) (8). Similarly, differential responses in lipids and lipoproteins by inflammatory status were observed following a Step I diet (9). In subjects with lower hs-CRP (<3.5 mg/L), LDL cholesterol (−3.5%) and the LDL-cholesterol:HDL-cholesterol ra-

tio (−4.8%) were reduced in response to Step I diets with added soy protein or milk protein. However, in those with higher hs-CRP (>3.5 mg/L), LDL cholesterol (+4.8%) and the LDL-cholesterol:HDL-cholesterol ratio (+5.2%) increased in response to Step I diets with added soy or milk protein. The authors reported that hs-CRP status was an independent predictor of the LDL cholesterol response to the Step I diet and explained 37% of the variance in the change in LDL cholesterol. Similar findings were observed in a randomized, crossover, controlled feeding study of diets higher in unsaturated fatty acids (14). The authors reported that apoB significantly decreased from baseline after 3 diets higher in unsaturated fat in those with lower hs-CRP (<1.2 mg/L) compared with no change in those with higher hs-CRP (≥ 1.2 mg/L). These studies suggest that greater diet-induced lipid/lipoprotein lowering occurs in individuals with less systemic inflammation, in the absence of any change in inflammatory status resulting from the dietary interventions.

There is also evidence to suggest that systemic inflammation can modulate diet-related changes in triglycerides. In a randomized, controlled-feeding study comparing a moderately low-fat diet with a high-fat diet rich in MUFAs, similar reductions in total and LDL cholesterol were observed after the 2 diets, with no change in hs-CRP (10). VLDL cholesterol, total triglycerides, and VLDL triglycerides were reduced after the high-MUFA diet; no change was observed after the lower fat diet. However, after the lower fat diet, total triglycerides and VLDL triglyceride concentrations were increased in those with higher hs-CRP (>1 mg/L). In contrast, reductions in total triglycerides and VLDL triglycerides were observed in those with low hs-CRP (<1 mg/L). In response to the high-MUFA diet, those with hs-CRP concentrations <1 mg/L had reductions in triglycerides, VLDL triglycerides, and VLDL cholesterol; however, reductions were not observed in those with higher hs-CRP concentrations at baseline. Similarly, in a trial of the DASH diet, subjects with a baseline hs-CRP concentration above the median had an increase in triglycerides (6). In subjects with higher baseline hs-CRP (>3 mg/L), a diet higher in PUFAs (9.7% of energy from PUFAs) lowered triglycerides (−11.7%) compared with a lower fat diet (31% of energy from fat), which increased triglycerides (+12.3%) (11). In subjects with low hs-CRP (<1 mg/L) at baseline, comparable triglyceride lowering was observed with the higher PUFA and lower fat diets, −28.9% and −29.1%, respectively. Thus, systemic inflammation can modulate the triglyceride response to changes in dietary macronutrient composition.

The presence of subclinical inflammation also affects postprandial lipidemia. Following consumption of a high-PUFA meal, subjects with hs-CRP >2 mg/L had a greater increase in postprandial triglycerides compared with those with hs-CRP <2 mg/L (13). There was no difference in postprandial hs-CRP, total cholesterol, LDL cholesterol, or HDL cholesterol between the hs-CRP subgroups. However, in subjects with low hs-CRP at baseline, cholesterol efflux was increased by 17% following the high-PUFA meal, whereas there was no change in cholesterol efflux in the subjects with higher hs-CRP at baseline. Blunted cholesterol efflux in the presence of inflammation was also observed in a randomized, controlled, crossover study of diets containing either 10% or 20% of energy from pistachios or a lower fat control diet (12). In this trial greater ATP-binding cassette transporter (ABC) A1-mediated serum cholesterol efflux capacity and global cholesterol efflux capability were only observed in subjects with low baseline hs-CRP (<1 mg/L)

TABLE 1 Studies that have reported secondary analyses examining lipid and lipoprotein lowering in response to blood cholesterol-lowering diets by inflammatory status of the subjects¹

Reference	Study design	Subjects	Treatment diets	Control diet	Duration	Reported results
Erlinger et al., 2003 (6)	Randomized, controlled-feeding	Healthy adults with BP 120–159/80–95 mmHg free of BP medication (n = 100)	DASH diet (27% fat, 6% SFA, 13% MUFA, 8% PUFA, 151 mg cholesterol)	Average American diet (37% fat, 16% SFA, 13% MUFA, 8% PUFA, 300 mg cholesterol)	30 d	DASH diet vs. control average American diet Lower hs-CRP group (<2.37 mg/L): ↓TC; ↓LDL-C; ↔TG Higher hs-CRP group (>2.37 mg/L): ↔TC; ↔LDL-C; ↑TG High-PUFA diets vs. average American control diet Lower hs-CRP (<2 mg/L) vs. higher hs-CRP (≥2 mg/L): ↓LDL-C (P = 0.068)
Zhao et al., 2004 (8)	Randomized, crossover, controlled-feeding	Men and women with moderately elevated cholesterol, 200–240 mg/dL (n = 23)	High-PUFA/high-LA diet (8% SFA, 16% PUFA, 12.6% LA, 3.6% ALA) High-PUFA/high-ALA diet (8% SFA, 16% PUFA, 10.5% LA, 6.5% ALA)	Average American diet (13% SFA, 13% MUFA, 9% PUFA)	6 wk	Diets collapsed into 1 group Lower hs-CRP (<3.5 mg/L): ↓LDL-C; ↓LDL-C:HDL-C Higher hs-CRP (>3.5 mg/L): ↑LDL-C; ↑LDL-C:HDL-C 10% pistachio diet vs. 20% pistachio diet Low hs-CRP group (<1 mg/L): ↑ABCA1-mediated cholesterol efflux capacity
Hilpert et al., 2005 (9)	Randomized, crossover, placebo-controlled, controlled-feeding	Healthy men and postmenopausal women with TC >204 mg/dL, LDL-C >50th percentile, TG <90th percentile (n = 32)	Step 1 diet (27% fat, 7% SFA, 275 mg cholesterol, 55% CHO, 29 g fiber) containing 25 g/d soy protein isolate + 90 mg isoflavones Diet with 10% energy from pistachios (58% CHO, 30% fat; 17% protein) Diet with 20% energy from pistachios (54% CHO, 34% fat, 17% protein)	Step 1 diet containing 25 g/d milk protein isolate Lower-fat diet (63% CHO, 25% fat; 15% protein)	6 wk	High-MUFA diet vs. lower-fat diet Lower hs-CRP group (<1 mg/L): ↑TG; ↓VLDL-C Higher hs-CRP group (>1 mg/L): ↑TG; ↑VLDL-C; ↑TC; ↓LDL-C Western diet vs. lower-fat control diet Lower hs-CRP group (<1 mg/L): ↔TG; ↔LDL-C; ↔HDL-C; ↔TC Higher hs-CRP group (>3 mg/L): ↑TG; ↔LDL-C; ↔HDL-C; ↔TC Western diet vs. high-PUFA diet Lower hs-CRP group (<1 mg/L): ↔TG; ↔LDL-C; ↔HDL-C; ↔TC Higher hs-CRP group (>3 mg/L): ↔TG; ↔LDL-C; ↔HDL-C; ↔TC
Holligan et al., 2014 (12)	Randomized, crossover, controlled-feeding	Healthy adults with elevated fasting LDL-C (>110 mg/dL, n = 18)	Diet with 10% energy from pistachios (58% CHO, 30% fat; 17% protein) Diet with 20% energy from pistachios (54% CHO, 34% fat, 17% protein)	Lower-fat diet (63% CHO, 25% fat; 15% protein)	4 wk	High-MUFA diet vs. lower-fat diet Lower hs-CRP group (<1 mg/L): ↑TG; ↓VLDL-C Higher hs-CRP group (>1 mg/L): ↑TG; ↑VLDL-C; ↑TC; ↓LDL-C Western diet vs. lower-fat control diet Lower hs-CRP group (<1 mg/L): ↔TG; ↔LDL-C; ↔HDL-C; ↔TC Higher hs-CRP group (>3 mg/L): ↑TG; ↔LDL-C; ↔HDL-C; ↔TC Western diet vs. high-PUFA diet Lower hs-CRP group (<1 mg/L): ↔TG; ↔LDL-C; ↔HDL-C; ↔TC Higher hs-CRP group (>3 mg/L): ↔TG; ↔LDL-C; ↔HDL-C; ↔TC
Desroches et al., 2006 (10)	Randomized, parallel, controlled-feeding	Healthy men (n = 65)	High-MUFA diet (45% CHO, 15% protein, 40% fat, 23% MUFA, 8% PUFA, 8% SFA)	Lower-fat diet (58% CHO, 16% protein, 26% fat, 13% MUFA, 5% PUFA, 6% SFA)	6–7 wk	High-MUFA diet vs. lower-fat diet Lower hs-CRP group (<1 mg/L): ↑TG; ↓VLDL-C Higher hs-CRP group (>1 mg/L): ↑TG; ↑VLDL-C; ↑TC; ↓LDL-C Western diet vs. lower-fat control diet Lower hs-CRP group (<1 mg/L): ↔TG; ↔LDL-C; ↔HDL-C; ↔TC Higher hs-CRP group (>3 mg/L): ↑TG; ↔LDL-C; ↔HDL-C; ↔TC Western diet vs. high-PUFA diet Lower hs-CRP group (<1 mg/L): ↔TG; ↔LDL-C; ↔HDL-C; ↔TC Higher hs-CRP group (>3 mg/L): ↔TG; ↔LDL-C; ↔HDL-C; ↔TC
St-Onge et al., 2009 (11)	Randomized, crossover, controlled-feeding	Adults with elevated LDL-C (130–180 mg/dL), TG <153 mg/dL, glucose <126 mg/dL (n = 33)	High-PUFA diet (49% CHO, 15% protein, 36% fat, 10% PUFA, 15% MUFA, 9% SFA) Lower-fat diet (55% CHO, 14% protein, 31% fat, 5% PUFA, 14% MUFA, 9% SFA)	Western diet (46% CHO, 16% protein, 38% fat, 6% PUFA, 16% MUFA, 11% SFA)	25 d	High-MUFA diet vs. lower-fat diet Lower hs-CRP group (<1 mg/L): ↑TG; ↓VLDL-C Higher hs-CRP group (>1 mg/L): ↑TG; ↑VLDL-C; ↑TC; ↓LDL-C Western diet vs. lower-fat control diet Lower hs-CRP group (<1 mg/L): ↔TG; ↔LDL-C; ↔HDL-C; ↔TC Higher hs-CRP group (>3 mg/L): ↑TG; ↔LDL-C; ↔HDL-C; ↔TC Western diet vs. high-PUFA diet Lower hs-CRP group (<1 mg/L): ↔TG; ↔LDL-C; ↔HDL-C; ↔TC Higher hs-CRP group (>3 mg/L): ↔TG; ↔LDL-C; ↔HDL-C; ↔TC

(Continued)

TABLE 1 (Continued)

Reference	Study design	Subjects	Treatment diets	Control diet	Duration	Reported results
Zhang et al., 2011 (13)	Randomized, crossover, controlled, postprandial	Healthy adults overweight or obesity and LDL \geq 110 mg/dL and TG < 350 mg/dL (n = 15)	34 g ground, defatted walnut meat, 51 g walnut oil, 5.6 g ground, defatted walnut skins	85 g ground walnuts	6 h (postprandial)	Diets collapsed into 1 group Lower hs-CRP (< 2 mg/L): \uparrow Cholesterol efflux; \downarrow SCD1 mRNA expression Higher hs-CRP (> 2 mg/L): \leftrightarrow Cholesterol efflux; \uparrow TG \leftrightarrow postprandial response DASH vs. all other diets Lower hs-CRP group (< 1 mg/L): \downarrow LDL-C Higher hs-CRP group (≥ 1 mg/L): \leftrightarrow LDL-C Beef containing diets vs. healthy American diet Lower hs-CRP group (< 1 mg/L): \leftrightarrow TC Higher hs-CRP group (≥ 1 mg/L): \downarrow TC
Roussel et al., 2012 (7)	Randomized, crossover, controlled-feeding	Healthy adults with elevated fasting LDL-C (110–176 mg/dL; n = 36)	DASH diet (55% CHO, 18% protein, 27% fat) Beef in an optimal lean diet (54% CHO, 19% protein, 28% fat) Beef in an optimal diet plus additional protein (45% CHO, 27% protein, 28% fat)	Healthy American diet (50% CHO, 17% protein, 33% fat)	5 wk	
Lee et al., 2018 (14)	Randomized, crossover, controlled-feeding	Healthy adults with overweight or obesity and elevated LDL-C (98–194 mg/dL)	Almond diet (48% CHO, 16% protein, 36% fat, 8% SFA, 16% MUFA, 9% PUFA) Chocolate diet (51% CHO, 16% protein, 33% fat, 12% SFA, 12% MUFA, 6% PUFA) Choc-almond diet (49% CHO, 16% protein, 35% fat, 9% SFA, 16% MUFA, 8% PUFA)	Average American diet (49% CHO, 17% protein, 34% fat, 13% SFA, 13% MUFA, 7% PUFA)	4 wk	Lower hs-CRP group (< 1.2 mg/L): \downarrow ApoB after the average American diet, almond diet, and choc-almond diet Higher hs-CRP group (≥ 1.2 mg/L): \leftrightarrow ApoB

¹ABCA1, ATP-binding cassette transporter A1; ALA, α -linolenic acid; BP, blood pressure; CHO, carbohydrate; DASH, Dietary Approaches to Stop Hypertension; HDL-C, HDL cholesterol; hs-CRP, high-sensitivity C-reactive protein; LA, linoleic acid; LDL-C, LDL cholesterol; SCD1, stearoyl CoA desaturase 1; Step 1, National Cholesterol Education Program Step 1 diet; TC, total cholesterol; TG, triglycerides; VLDL-C, VLDL cholesterol; \uparrow , increased; \downarrow , decreased; \leftrightarrow , no change.

after consumption of the diet containing 20% of energy from pistachios compared with the diet containing 10% of energy from pistachios (12). These studies suggest that low-grade inflammation augments postprandial lipidemia and blunts cholesterol efflux.

Lipid and Lipoprotein Responses to Dietary Interventions in the Presence of Excess Adiposity and Insulin Resistance

Excess adiposity blunts lipid and lipoprotein responsiveness to dietary intervention, as reviewed previously (23, 24). Notably, a recent trial that a priori aimed to compare the effect of replacing saturated fat with PUFAs in healthy weight (BMI ≤ 25 kg/m²) and obese (BMI 30–45) individuals, with similar baseline LDL cholesterol (~ 169 mg/dL), showed heterogeneity by baseline BMI group ($P = 0.02$) (25). In this trial the normal-weight subjects had a reduction in LDL cholesterol of 10.4% (95% CI: $-15.2, -5.7\%$) whereas the subjects with obesity had a nonsignificant reduction of 2.3% (95% CI: $-7.4, 2.8\%$); similar effect modification by BMI was observed for apoB. There was no difference in the change in LDL cholesterol by BMI when the subjects were on the control diet higher in saturated fat; however, total cholesterol increased more with the control diet ($P = 0.010$) in the healthy-weight subjects (8.6%; 95% CI: 4.3, 12.9%) compared to the subjects with obesity (2.0%, 95% CI: $-2.3, 6.3\%$). In this study, the subjects with obesity had higher hs-CRP concentrations at baseline, in addition to lower HDL cholesterol and higher triglycerides, which could be indicative of insulin resistance. Thus, the underlying cause of the differential responsiveness to replacement of saturated fat with unsaturated fat in the study cannot be disentangled; however, this study, which was designed with the intent of characterizing diet responsiveness in individuals of a lean healthy weight compared to those with obesity, was much needed to confirm the many exploratory analyses previously conducted.

Overweight and obesity are inflammatory conditions. Furthermore, excess adiposity and inflammation are implicated in the etiology of insulin resistance (26). Overweight and obesity increase the risk of ectopic lipid accumulation and desensitization of insulin signaling in the skeletal muscle (27). Insulin resistance is marked by decreased insulin-stimulated glucose uptake in muscle, excess or inappropriate hepatic glucose production, and lipolysis in adipose tissue because of reduced insulin-mediated inhibition (28). Secondary analyses of randomized controlled trials have shown that the presence of insulin resistance modulates lipid and lipoprotein responses to dietary interventions (Table 2). These 5 trials were identified using nonsystematic search strategies to identify clinical trials that measured lipids and lipoproteins in response to a dietary intervention and reported results by insulin resistance status.

Some evidence suggests that individuals with insulin resistance are hyporesponsive to increased consumption of dietary cholesterol compared with those who are insulin sensitive. In a crossover study, subjects who were insulin sensitive ($n = 65$), insulin resistant ($n = 75$), or had obesity and were insulin resistant ($n = 57$) were randomly assigned to consume a Step I diet with 0, 2, or 4 eggs per day for 1 mo (15). Following consumption of 2 and 4 eggs per day, the insulin-sensitive subjects had the greatest increase from baseline in total cholesterol (2.2% and 6.2%, respectively) and HDL cholesterol (5.5% and 8.8%, respectively);

the change in HDL cholesterol was less pronounced in those with obesity and insulin resistance (-0.2% and 3.6% , respectively). In response to consumption of 4 eggs per day, LDL cholesterol was increased from baseline in the insulin-sensitive (7.8%) and insulin-resistant subjects (3.3%), but no significant change was observed in the insulin-resistant subjects with obesity. In the insulin-sensitive subjects, a reduction in triglycerides was observed after consumption of 4 eggs per day (-5.5%); no significant difference was observed in the insulin-resistant subjects with or without obesity. This reduction in triglycerides was likely because of displacement of dietary carbohydrates by the high egg intake, but this finding was not observed in the insulin-resistant group. In contrast, no change in total cholesterol or LDL cholesterol was observed in insulin-sensitive and insulin-resistant postmenopausal women, after 4 wk, when dietary cholesterol was increased from 113 mg/d to 319, 523, or 941 mg/d as part of a Step I diet (29). However, in this study only 8–11 women were included in each treatment subgroup, and thus it could have been underpowered to detect a differential response based on insulin sensitivity. Furthermore, the discrepancy in findings could be partially explained by the influence of the fatty acid composition of the diets provided (15, 29).

In the controlled feeding study conducted by Reaven and colleagues (29) the diets were matched for total fat, saturated fat, and PUFAs. However, Knopp et al. (15) provided egg preparations that differed in total fat content (saturated fat content not reported but likely differed) and education to follow a Step I diet. Therefore, it is unlikely that the diets were fatty acid matched, which could account for the differences in the results obtained. Together these studies suggest that fatty acid-matched diets differing in dietary cholesterol might not elicit differential lipid and lipoprotein responses in individuals who are insulin sensitive compared with those who are insulin resistant; however, insulin resistance can affect responsiveness to diets with differing macronutrient and fatty acid compositions. This is consistent with the observation that saturated fat increases total cholesterol and LDL cholesterol to a greater extent than dietary cholesterol (30, 31).

A 6-mo randomized controlled trial examined the effect of dietary composition on lipids and lipoproteins, and showed insulin-sensitive subjects had greater LDL-cholesterol lowering in response to a high-fat diet containing walnuts compared with subjects with insulin resistance (-15 mg/dL compared with -7 mg/dL) (16). Total cholesterol declined significantly from baseline after all 3 diets (i.e., lower fat, high-fat, high-fat walnut-rich), except in the insulin-resistant subjects on the high-fat diet. Similarly, in a 3-period, randomized, crossover study examining lipid and lipoprotein responses to a Step I diet (30% fat, 9% saturated fat), a Step II diet (25% fat, 6% saturated fat), and a control average American diet (38% fat, 14% saturated fat), the presence of insulin resistance modulated the lipid/lipoprotein response (17). The Step I and Step II diets lowered total cholesterol and LDL cholesterol compared with the control average American diet in the whole cohort. However, when the cohort was divided by the median fasting insulin concentration (6.8 μ U/mL), diminished cholesterol lowering (-58%) was observed in subjects with greater fasting insulin concentrations, compared with those below the median, following a Step II diet. A similar attenuation in LDL cholesterol lowering was observed with increasing HOMA-IR. Finally, increased insulin concentrations attenuated the LDL cholesterol response to a greater extent than excess adiposity; subjects with a BMI above the median (≥ 25.3) had 30% less LDL cholesterol

TABLE 2 Studies that have reported secondary analyses examining lipid and lipoprotein lowering in response to blood cholesterol-lowering diets by insulin sensitivity status¹

Reference	Study design	Subjects	Treatment diets	Control diet	Duration	Reported results
Reaven et al., 2001 (29)	Randomized, partial crossover, controlled-feeding study (each subject received the control diet and 1 treatment diet)	Postmenopausal women who were insulin sensitive (<i>n</i> = 32) or insulin resistant (<i>n</i> = 33) assessed by insulin suppression test (IS: steady-state plasma glucose <100 mg/dL; IR: steady-state plasma glucose >160 mg/dL)	Step 1 diet containing 319 mg/d, 523 mg/d, or 941 mg/d cholesterol	Step 1 diet containing 113 mg/d cholesterol	4 wk	↔ TC or ↔ LDL-C by insulin sensitivity status or dietary cholesterol intake
Knopp et al., 2003 (15)	Randomized, double-blinded, 3-period, crossover study	Insulin sensitive (<i>n</i> = 65), insulin resistant (<i>n</i> = 75), or obese insulin resistant (<i>n</i> = 57) assessed by the insulin-sensitivity index (IS: $\geq 4.2 \cdot 10^{-4} \text{ min}^{-1} \mu\text{U/mL}$; IR: $< 4.2 \cdot 10^{-4} \text{ min}^{-1} \mu\text{U/mL}$)	Education to following a Step 1 diet, and provision of a preparation comprising 0, 2, or 4 eggs/d	N/A	1 mo	0 eggs/d: IS: ↔ TC; ↔ TG; ↔ LDL-C; ↔ HDL-C; ↔ non-HDL-C IR: ↓ TC; ↔ TG; ↔ LDL-C; ↔ HDL-C; ↓ non-HDL-C OIR: ↔ TC; ↔ TG; ↔ LDL-C; ↔ HDL-C; ↔ non-HDL-C 2 eggs/d: IS: ↑ TC; ↔ TG; ↔ LDL-C; ↑ HDL-C; ↔ non-HDL-C IR: ↔ TC; ↔ TG; ↔ LDL-C; ↑ HDL-C; ↔ non-HDL-C OIR: ↑ TC; ↔ LDL-C; ↑ HDL-C; ↔ TG; ↔ non-HDL-C ↑ HDL-C in the IS vs. OIR (<i>P</i> < 0.01) 4 eggs/d: IS: ↑ TC; ↑ TG; ↑ LDL-C; ↑ HDL-C; ↑ non-HDL-C IR: ↑ TC; ↔ TG; ↑ LDL-C; ↑ HDL-C; ↔ non-HDL-C OIR: ↑ TC; ↔ TG; ↔ LDL-C; ↑ HDL-C; ↔ non-HDL-C ↑ TC and ↑ HDL-C in IS vs. OIR (<i>P</i> < 0.05)

(Continued)

TABLE 2 (Continued)

Reference	Study design	Subjects	Treatment diets	Control diet	Duration	Reported results
Lefevre et al., 2005 (17)	Randomized, double-blind, 3-period crossover controlled feeding study	Healthy men (n = 86)	Step I diet (30% fat, 9% SFA) and Step II diet (25% fat, 6% SFA)	Average American control diet (38% fat, 14% SFA)	6 wk	Fasting insulin above the median reduced LDL-C lowering by 42% vs. fasting insulin less than the median. The difference in TC after the average American diet vs. the Step I and Step II diet was correlated with baseline fasting insulin and HOMA-IR. The difference in LDL-C between the Step II diets and the control diet was correlated with fasting insulin. HOMA-IR tertile 1 (<1.90): LFHCC vs. other 3 diets: ↓LDL-C; ↓TG Difference between 4 diets: ↔→TC LFHCC n-3 and LFHCC diets vs. HSFA and HMUFA diets: ↓BMI; ↓WC HSFA diet vs. HMUFA and LFHCC n-3 diet: ↑HOMA-IR; ↑fasting insulin HMUFA and LFHCC n-3 diet vs. HSFA and LFHCC diet: ↓IL-6 HMUFA and LFHCC n-3 diet vs. HSFA and LFHCC diet: ↓IL-6 HOMA-IR tertile 2 (1.90–2.93): LFHCC n-3 vs. other 3 diets: ↓TG LFHCC n-3 and LFHCC diets vs. HSFA and HMUFA diets: ↓BMI HMUFA and LFHCC n-3 diet vs. HSFA and LFHCC diets: ↓IL-6 Difference between 4 diets: ↔→LDL-C; ↔→TC; ↔→HOMA-IR; ↔→fasting insulin; ↔→WC HOMA-IR tertile 3 (>2.93): Difference between 4 diets: ↔→LDL-C; ↔→TG; ↔→TC; ↔→WC; ↔→BMI; ↔→IL-6 HMUFA and LFHCC n-3 diets vs. HSFA diet: ↓HOMA-IR; ↓fasting insulin
Yubero-Serrano et al., 2015 (32)	Randomized, 4-arm, parallel study	Adults with metabolic syndrome (n = 472) stratified by tertile of baseline HOMA-IR (<1.9; 1.9–2.93; >2.93)	Education to follow 1 of 4 diets: 1) High-SFA (HSFA) diet (38% energy; 16% SFA, 12% MUFA, and 6% PUFA) 2) High-MUFA (HMUFA) diet (38% energy; 8% SFA, 20% MUFA, and 6% PUFA) 3) LFHCC (low-fat, high-complex CHO) n-3 diet (28% energy, 8% SFA, 11% MUFA, 6% PUFA, plus 1.24 g/d n-3 PUFA) 4) LFHCC control diet (28% energy, 8% SFA, 11% MUFA, and 6% PUFA), plus a control high-oleic acid sunflower seed oil capsule (4 × 1-g capsules/d)	N/A	12 wk	

(Continued)

TABLE 2 (Continued)

Reference	Study design	Subjects	Treatment diets	Control diet	Duration	Reported results
Le et al., 2016 (16)	Randomized, 3-arm parallel study	Overweight or obese women who were insulin sensitive (n = 119) or insulin resistant (n = 126) assessed by HOMA (IS: ≤3; IR: >3)	Education to follow 1 of 3 diets: 1) Lower fat (20% energy), higher CHO (65% energy) diet 2) Higher fat (35% energy), lower CHO (45% energy) diet 3) Walnut-rich (18% energy), higher fat (35% energy), CHO (45% energy) diet	N/A	6 mo	Lower fat: IS: ↓TC; ↓TG; ↓HDL-C; ↔LDL-C IR: ↓TC; ↓TG; ↓HDL-C; ↔LDL-C Lower carbohydrate: IS: ↓TC; ↓TG; ↔HDL-C; ↔LDL-C IR: ↔TC; ↓TG; ↔HDL-C; ↔LDL-C ↔LDL-C Walnut-rich: IS: ↓TC; ↓TG; ↑HDL-C; ↓LDL-C IR: ↓TC; ↓TG; ↑HDL-C; ↔LDL-C ↓Insulin all diets and conditions

¹CHO, carbohydrate; HDL-C, HDL cholesterol; HMUFA, high-MUFA; HSA, high-SFA; IR, insulin resistant; IS, insulin sensitive; LDL-C, LDL cholesterol; LFHCC, low-fat, high-complex carbohydrate; N/A, not applicable; OIR, obese insulin resistant; Step I/II, National Cholesterol Education Program Step I/II (diet); TC, total cholesterol; TG, triglycerides; WC waist circumference; ↑, increased; ↓, decreased; ↔, no change.

lowering compared with subjects with a BMI less than the median (29). Thus, insulin resistance can lessen the impact of dietary interventions aimed at improving the lipid and lipoprotein profile to a greater extent than excess adiposity.

In the LIPGENE study, a 12-wk multicenter randomized controlled trial conducted in 8 European locations, subjects in the lowest HOMA-IR tertile (<1.90) had a reduction in LDL cholesterol and triglycerides following consumption of a low-fat diet enriched with ω -3 fatty acids compared with the other 3 treatment diets, which were high in saturated fat, high in MUFAs, and low-fat (32). However, in tertiles 2 (HOMA-IR 1.90–2.93) and 3 (HOMA-IR >2.93) there was no difference in the change in total or LDL cholesterol with the diets differing in fatty acid composition. In tertile 2, a reduction in triglycerides was observed with the low-fat diet supplemented with ω -3 fatty acids compared with the 3 other diets. Interestingly, the high-MUFA diet and the low-fat diet supplemented with ω -3 fatty acids improved HOMA-IR and fasting insulin concentrations compared with the high-saturated-fat diet only in subjects with the greatest level of insulin resistance (HOMA-IR tertile 3); no changes were observed in tertiles 1 or 2. In contrast, IL-6 was reduced after the high-MUFA diet and the low-fat diet supplemented with ω -3 fatty acids, compared with the high-saturated-fat diet and the low-fat diet, in subjects in HOMA-IR tertiles 1 and 2 only; no change was observed in tertile 3. This study provides further evidence that insulin sensitivity modulates LDL-cholesterol lowering in response to dietary intervention and suggests that diet-induced improvement in HOMA-IR does not result in the concurrent lowering of LDL cholesterol over a 12-wk period. Thus, it is hypothesized that HOMA-IR and LDL cholesterol-lowering dietary interventions can be most effective when implemented for a longer duration or consecutively.

Potential Mechanisms to Explain How Inflammation and Insulin Resistance Might Modify Lipid/Lipoprotein Metabolism and Responsiveness to Dietary Intervention

Reviewed herein is evidence from secondary analyses of randomized controlled trials that have reported subgroup analyses examining responsiveness by level of inflammation or insulin sensitivity. The trials identified suggest that individuals with greater systemic inflammation or insulin resistance have diminished LDL-cholesterol lowering in response to diets designed to lower lipids/lipoproteins compared with noninflamed or insulin-sensitive individuals. Differential responses were also observed for triglyceride lowering. It is acknowledged that low-grade inflammation and insulin resistance might be discrete phenotypes; however, they can co-occur and the data available do not enable us to examine the relative contributions of each state to the altered lipid and lipoprotein responsiveness observed in these dietary studies. Furthermore, given the exploratory nature of the analyses presented, the findings must be interpreted with caution and require replication in trials where these analyses are planned a priori. In addition, the evidence reviewed is likely affected by publication bias because the results of subgroup analyses not reaching statistical significance might not have been published. However, these findings are biologically plausible based on a number of known disturbances to cholesterol metabolism that occur in the presence of elevated concentrations of circulating proinflammatory molecules and insulin resistance. The

TABLE 3 Proposed mechanisms by which individuals with low-grade inflammation or insulin resistance could have a blunted lipid and lipoprotein response to cholesterol-lowering diets¹

Inflammation blunts cholesterol efflux:

- Modulates SCD1, ABCA1 and ABCG1, and SR-B1
- Induces HDL-cholesterol remodeling

Inflammation alters genes involved in endogenous cholesterol synthesis and cholesterol uptake:

- Reduces LDL-cholesterol clearance by upregulating PCSK9 expression
- Alters LDL-R expression by modulating transcription factors from the SREBP and HNF1 α families

Insulin and inflammatory cytokines increase PCSK9 production by SOCS3-dependent pathways and upregulate de novo lipogenesis:

- Insulin induces SOCS3, which upregulates SREBP-1c expression and enhances fatty acid synthesis
- Proinflammatory cytokines increase SOCS3 protein expression; and SOCS3 is required for the TNF- α induction of PCSK9

¹ABC, ATP-binding cassette transporter; HNF1 α , hepatocyte nuclear factor-1 α ; LDL-R, LDL receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; SCD1, stearoyl CoA desaturase 1; SOCS3, suppressor of cytokine signaling-3; SR-B1, scavenger receptor class B type; SREBP, sterol regulatory element binding protein.

subsequent sections describe alterations that occur to pathways involved in cholesterol homeostasis, including cholesterol efflux, cholesterol synthesis, and de novo lipogenesis, with inflammation and/or insulin resistance (Table 3). In addition, the emerging role of proprotein convertase subtilisin/kexin type 9 (PCSK9) in these altered responses is discussed because it provides a biologically plausible link between inflamed and insulin-resistant states and blunted lipid and lipoprotein responses to traditional blood cholesterol-lowering diets.

Inflammation blunts cholesterol efflux

A proinflammatory state might modulate cholesterol metabolism through attenuation of cholesterol efflux, a process that is essential to maintaining cellular cholesterol homeostasis and the first step in reverse cholesterol transport (33). As described previously, the benefits of walnuts and pistachios on cholesterol efflux were only apparent in individuals with lower hs-CRP concentrations (12, 13). In an investigation of the potential mechanisms underlying the findings, it was found that the hs-CRP subgroups had differences in THP-1 (human monocytic cell line) foam cell stearoyl CoA desaturase 1 (SCD1), with a more pronounced reduction in SCD1 gene expression and protein concentrations in the low-hs-CRP group (13). SCD1 catalyzes bioconversion of saturated fat to MUFAs, with evidence to suggest additional potential function in inhibition of cholesterol efflux to apoA1 (34). The investigators suggested that the inhibition of SCD1 by the PUFAs in walnuts played a role in increasing cholesterol efflux (13). Subsequent investigation of regulatory pathways indicated that α -linolenic acid activates the nuclear receptor farnesoid-X receptor to increase expression of the target gene, small heterodimer partner (SHP); SHP has a repressive effect on liver-X receptor (LXR)-mediated transcription of SCD1 through the LXR target, sterol regulatory element binding protein (SREBP) 1c (35). SCD1 activity is an independent predictor of hs-CRP concentrations in men (36), and is positively associated with hs-CRP in humans, independent of obesity and lifestyle factors (36, 37). Although this might reflect a link between lipogenic activity and inflammation, the relation between SCD1 and inflammation in macrophages is controversial, with conflicting findings reported between human and animal studies (38).

Alternatively, the relation between inflammatory status and cholesterol efflux following dietary intervention could be because of modulation of key molecules that directly mediate efflux, such as the ABCA1 and ABCG1, and the scavenger receptor class B type 1 (SR-B1). In vitro models demonstrate that CRP decreases cholesterol efflux from human

THP-1-derived and peripheral blood mononuclear cell-derived foam cells to apoA1 and HDL particles (39). ABCA1 and ABCG1 gene expression were downregulated in a concentration-dependent manner coincident with protein concentration, suggesting that CRP might inhibit efflux by modulating these cholesterol and phospholipid transporters. In vitro models of LPS-treated human monocyte-derived macrophages show a reduction in cholesterol efflux to apoA1 and serum, but not HDL3 (40). Although the LPS treatment reduced ABCA1, ABCG1, and SR-B1 mRNA expression, protein concentrations of ABCA1 and SR-B1 were substantially and modestly lowered, respectively, with no effect on ABCG1. However, direct comparison between in vitro CRP and LPS studies is limited, because the models provide unique assessment of chronic compared with acute inflammation. In contrast, no differences in ABCA1 or ABCG1 protein concentrations were observed between hs-CRP subgroups following efflux assays using sera from walnut-treated humans, although ABCA1 mRNA was lower in the high-hs-CRP group (13).

Inflammatory-mediated alteration of extracellular acceptor function might also attenuate cholesterol efflux, with evidence to suggest that inflammation causes HDL-cholesterol remodeling. Endotoxemia induced by LPS exposure in rodents decreased apoA1 and increased the content of the acute-phase protein serum amyloid A (SAA) in HDL (40). An LPS challenge in humans impaired HDL efflux capacity, with a strong inverse correlation between SAA composition in HDL and cholesterol efflux capacity (41). Recently, Ronsein and Vaisar (42) reviewed the effects of inflammation on HDL composition and concluded that acute inflammation causes HDL remodeling, particularly through enrichment of SAA, to impair cholesterol efflux; however, chronic inflammation might have differing and subtle effects on cholesterol acceptors.

Evidence suggests that inflammation blunts cholesterol efflux, with numerous underlying pathways proposed. Taken together, additional research is necessary to identify the mechanisms by which inflammation, and in particular low-grade chronic inflammation, attenuates cholesterol efflux.

Inflammation and hyperinsulinemia upregulate PCSK9 expression

In cholesterol homeostasis, LDL receptors (LDL-R) and PCSK9 are expressed in response to upregulation of SREBP-2 because of low intracellular cholesterol concentrations, which can occur following consumption of a diet low in saturated fat (43, 44). This increases

hepatic LDL-R-mediated uptake of LDL cholesterol and reduces circulating concentrations. PCSK9 binds to hepatic LDL-R intracellularly, routing the receptor toward lysosomal degradation, or on the cell surface, causing degradation when endocytosed (45). This prevents recycling of the LDL-R to the cell surface, thereby attenuating LDL-cholesterol clearance. Thus, this reciprocal relation between LDL-R and PCSK9 results in the maintenance of stable circulating LDL-cholesterol concentrations (43). However, with greater expression of PCSK9, fewer LDL-Rs are available, and more LDL cholesterol remains in the circulation. Experimental evidence suggests that inflammation and hyperinsulinemia can increase PCSK9 expression through transcription factors from the SREBP (44) and hepatocyte nuclear factor-1 α (HNF1 α) families (46, 47).

Insulin and PCSK9 and lipid metabolism

Insulin induces suppressor of cytokine signaling-3 (SOCS3) (48), which upregulates SREBP-1c expression for subsequent enhancement of fatty acid synthesis (49, 50). In vitro evidence shows that SOCS3 overexpression in HepG2 cells results in greater mRNA expression and protein abundance of fatty acid synthase and SCD-1, and greater apoB concentrations and accumulation of intracellular triglycerides (51). Thus, metabolic alterations because of insulin resistance lead to increases in hepatic production of free fatty acids and triglycerides, and increased VLDL-cholesterol production (52–54). The increased hepatic synthesis of triglycerides in the presence of insulin resistance might explain the lack of triglyceride lowering observed when carbohydrates were displaced by 4 eggs per day in individuals who were insulin resistant; triglyceride lowering, in contrast, was observed in insulin-sensitive individuals (15).

SOCS3 has also been shown to increase PCSK9 mRNA and protein in HepG2 cells by suppression of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway (51). This is consistent with murine experiments showing that hepatic PCSK9 and SREBP-1c mRNA expression and protein concentrations were increased in response to insulin, but not glucose (55). Thus, in the presence of hyperinsulinemia it is likely that there is reduced clearance of LDL cholesterol because of upregulation of PCSK9. However, insulin also increases LDL-R expression (56). Therefore, it is possible that the lack of LDL-cholesterol lowering observed in the insulin-resistant state is because of the reciprocal relation between LDL-R and PCSK9, which maintains stable circulating LDL-cholesterol concentrations and attenuates LDL-cholesterol lowering.

SOCS3 protein expression is increased by proinflammatory cytokines including IL-6 and TNF- α (57), and experiments using HepG2 cells show that SOCS3 is required for the TNF- α induction of PCSK9 (51). Similarly, increased apoB concentrations were observed in a hepatic cellular model of SOCS3 overexpression, which suggests that PCSK9 has a role in apoB production (51). Studies in mouse models show that PCSK9 expression increases apoB, independent of the presence of LDL-R, and PCSK9 interacts with apoB and reduces its degradation (58). This results in increased production and secretion of apoB and apoB-containing lipoproteins, including LDL cholesterol and VLDL cholesterol. Therefore, the combination of hyperinsulinemia and elevated concentrations of inflammatory cytokines might increase PCSK9 production by SOCS3-dependent pathways and result

in upregulation of de novo lipogenesis and increased production of apoB.

Inflammation, PCSK9, and lipid metabolism

Observational evidence shows that higher systemic inflammation is associated with increased PCSK9 (59–61). In support of this, in vivo animal and in vitro human-derived cell model studies show that inflammation increases PCSK9. Administration of an inflammatory stimulus, LPS, increased hepatic PCSK9 mRNA expression in mice (62, 63), along with plasma lipids and inflammatory cytokines (63). Human CRP increased PCSK9 protein abundance and mRNA expression and suppressed LDL-R expression in HepG2 cells (47). Likewise, TNF- α induced expression of PCSK9 mRNA and protein levels in HepG2 cells (51).

Inflammation can result in the upregulation of PCSK9 expression through SREBP-2-dependent pathways. SREBP-2 is a transcription factor that modulates cholesterol homeostasis by regulating genes involved in endogenous cholesterol synthesis and cholesterol uptake, including both LDL-R and PCSK9. SREBP-2 binds to the sterol regulatory element (SRE) in the promoter region of these target genes to upregulate transcription (44). However, in LPS-injected mice fed a high-cholesterol diet, hepatic LDL-R mRNA expression decreased, as expected, whereas PCSK9 mRNA expression significantly increased (62). Thus, the inflammatory stimuli led to upregulation of PCSK9, and the discordance in LDL-R and PCSK9 expression in response to the high-cholesterol diet suggests that SREBP-2 did not mediate the inflammation-induced upregulation of PCSK9 (62). Alternatively, a binding site for the transcription factor HNF1 α is also present in the PCSK9 promoter region, but is absent from the LDL-R promoter (46). Cui and colleagues (47) provided evidence that treatment of human hepatoma HepG2 cells with CRP increases PCSK9 expression and protein concentrations, while decreasing expression and protein concentrations of LDL-R. In this study, CRP treatment of HepG2 cells increased HNF1 α protein, but not SREBP-2 or SREBP-1, suggesting the increase in PCSK9 occurred through activation of the p38 mitogen-activated protein kinase (p38MAPK)-HNF1 α pathway (47). In support of this, treatment of the HepG2 cells with a p38MAPK inhibitor reduced CRP-induced nuclear HNF1 α protein concentrations. However, HNF1 α -dependent pathways do not explain the CRP-induced suppression of LDL-R expression, because there is no binding site for HNF1 α on the LDL-R promoter; this requires further research. In summary, these studies suggest that inflammation upregulates PCSK9 expression through pathways independent of SREBP-2 when intracellular cholesterol concentrations are adequate and SREBP-2 is suppressed. However, when intracellular sterol concentrations are low (e.g., following consumption of a cholesterol-lowering diet) upregulation of SREBP-2 occurs, although the presence of inflammation might reduce LDL-R expression and increase PCSK9 expression through HNF1 α -dependent pathways.

The experimental evidence presented in this section suggests that systemic inflammation and insulin resistance can disrupt LDL-cholesterol clearance by upregulating PCSK9 expression and altering LDL-R expression, which could, in part, explain the diminished LDL-cholesterol lowering observed in response to blood lipid/lipoprotein-lowering dietary interventions. However, we cannot discount the possibility of alternative and/or complementary pathways.

Future Directions and Conclusions

Individual variation in responsiveness to treatment (pharmacological and nonpharmacological), particularly lipid-lowering, is well established (64–67), and the evidence reviewed suggests that the insulin-resistant and/or chronically inflamed phenotype can be a source of variation in lipid/lipoprotein lowering with dietary intervention. The well-described interindividual variation in response to both pharmacological and nonpharmacological treatments is the basis for the emergence of precision medicine. However, precision medicine is in the early stages of development, and aims to provide the optimal treatment for an individual at the right time based on multiple pieces of information about the individual including, but not limited to, phenotype, genotype, epigenetics, and the microbiome (68). Currently, science is not at a point where personalized, evidence-based nutrition can be delivered at scale (69). Precision public health, defined as the identification and provision of the right treatment for the right population at the right time, is more relevant to the current environment and public health challenges (70, 71). In this approach, a population with inflammation and/or insulin resistance would be treated differently to those who do not present with these phenotypes.

Grouping individuals based on their metabolic phenotype, termed metabotype, is an emerging concept and could be particularly relevant to nutritional management of disease risk; however, there have been few empirical investigations of metabotype-specific responses to date (72, 73). Further research establishing the interindividual variation and predictors of lipid and lipoprotein responsiveness to dietary intervention is needed. This will require clinical trials that a priori define subgroups of interest and appropriately plan for this in the study design (i.e., by specifying stratification factors and building this into the randomization scheme and statistical plan). This is in contrast to conducting exploratory analyses during the data analysis phase to determine if any subgroups of the study cohort differed, which historically is the most common method of identifying variation. These types of analyses should be interpreted cautiously and treated as hypothesis-generating. Future investigations examining effect modification by inflammation should also ensure the inflammatory and/or insulin resistant phenotype is well defined.

All of the studies we identified used hs-CRP to assess inflammation status, which is an acute-phase reactant and has high within- and between-subject variability. To account for the within-subject variability, it is recommended that 2 separate hs-CRP measurements are taken to characterize inflammatory status (74). The trials we reviewed used a single hs-CRP measurement at baseline to determine inflammation status (6–14). In addition, a wide range of hs-CRP cut-points were used in the reviewed studies to define higher compared with lower inflammation, which precludes conclusions about the hs-CRP concentration that affects diet-induced lipid/lipoprotein lowering. The 2018 AHA/American College of Cardiology Guideline on the Management of Blood Cholesterol lists hs-CRP >2 mg/L as an atherosclerotic CVD risk enhancer (2). Use of this cut-point in future studies could help with standardization and reduce cut-point–related heterogeneity.

Similarly, there are many methods available to assess insulin sensitivity, and a number of factors should be considered when selecting the most appropriate method for the research aim and population being studied (75). Three of the 5 trials we identified that exam-

ined lipid/lipoprotein responsiveness to dietary intervention by insulin sensitivity used surrogate markers defined from fasting samples (i.e., HOMA or fasting insulin) (16, 17, 32). HOMA primarily reflects hepatic insulin sensitivity, and thus an assumption is that hepatic and peripheral insulin sensitivity are proportional (75). One trial used fasting insulin (17), which is limited by the lack of standardization of the insulin assay. In addition, fasting insulin might not accurately reflect insulin sensitivity in individuals with diabetes because of impairments to insulin secretion (75). One trial used an indirect measure of insulin sensitivity (15), frequently sampled intravenous-glucose tolerance test, which is less reliable in individuals with impaired insulin secretion and/or significant insulin resistance (75). Only 1 trial used a direct measure of insulin sensitivity (29). Future studies should ensure that appropriate and reliable methods, for the population being studied, are used to assess insulin sensitivity. At present, standardized cut-points are not used to define insulin resistance, which poses a challenge for planning future studies to examine heterogeneity in diet-induced lipid/lipoprotein lowering by insulin resistance status.

This review presents findings from secondary analyses of randomized controlled trials and collectively the evidence suggests diminished lipid and lipoprotein lowering in response to dietary interventions, with established lipid-lowering effects, in individuals with inflammation and/or insulin resistance. Experimental studies show inflammatory stimuli and insulin alter expression of LDL-R, increase expression of PCSK9, reduce cholesterol efflux, and increase fatty acid biosynthesis, which provide biological plausibility to these clinical observations. However, to date very few clinical trials have been designed a priori to characterize interindividual variation in diet responsiveness; these types of trials are required to confirm these experimental and clinical findings. A greater understanding of how inflammation and/or insulin resistance modulates lipid and lipoprotein responsiveness to dietary intervention could improve the management of CVD risk in individuals presenting with these phenotypes.

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