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REVIEW

Pharmacological effects of lipid-lowering drugs on circulating adipokines

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Abstract

The cardioprotective effects of lipid-lowering drugs have been primarily attributed to their effects on blood lipid metabolism. However, emerging evidence indicates that lipid-lowering drugs also modulate the synthesis and secretion of adipose tissue-secreted proteins referred to as adipokines. Adipokines influence energy homeostasis and metabolism and have also been shown to modulate the vascular inflammatory cascade. The purpose of this review will be to examine the reported effects of commonly used lipid-lowering drugs (statins, fibrates, niacin and omega-3-fatty acids) on the circulating concentrations of leptin, adiponectin, tumor necrosis-factor-α (TNF-α), Retinol binding protein 4 (RBP4) and resistin. Overall, the lipid-lowering drugs reviewed have minimal effects on leptin and resistin concentrations. Conversely, circulating adiponectin concentrations are consistently increased by each lipid-lowering drug reviewed with the greatest effects produced by niacin. Studies that have examined the effects of statins, niacin and omega-3-fatty acids on TNF-α demonstrate that these agents have little effect on circulating TNF-α concentrations. Niacin and fibrates appear to lower RBP4 but not resistin concentrations. The results of the available studies suggest that a strong relationship exists between pharmacological reductions in blood lipids and adiponectin that is not obvious for other adipokines reviewed.

Key words: Statins; Fibrates; Niacin; Omega-3 fatty acids; Adipokines; Leptin; Adiponectin; Cardiovascular disease; Hyperlipidemia

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INTRODUCTION

The incidence of obesity has increased by more than two-fold over the past 30 years[1]. Indeed, nearly two-thirds of the US population are considered overweight or obese by current criteria. Obesity is associated with a clustering of metabolic and cardiovascular disease (CVD) risk factors referred to as the metabolic syndrome which includes hypertension, insulin resistance, and atherogenic dyslipidemia. While the practical significance and criteria for metabolic syndrome continue to be debated, treatment primarily focuses on individual risk factors. Atherogenic dyslipidemia is characterized by moderately elevated low-density lipoprotein-cholesterol

(LDL-C, 130-159 mg/dL), elevated triglycerides (> 150 mg/dL), small LDL particles and low high-density lipoprotein-cholesterol (HDL-C, < 35 mg/dL)[2]. The primary pharmacological strategies for the treatment of atherogenic dyslipidemia are the 3-hydroxy-3-methylg lutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). The use of statins for the treatment of dyslipi demia is based on consistent evidence from a number of clinical trials that LDL-C is the predominant atherogenic lipoprotein[3]. However, statins are often not the optimal treatment for atherogenic dyslipidemia when used alone due to their ineffectiveness at lowering serum triglycerides and raising HDL-C. Other pharmacological agents such as fibrates, niacin and omega-3 fatty acids are routinely used in combination with statins or alone and have proven to independently reduce atherogenic dyslipidemia and CVD morbidity and mortality[4-6]. Although the primary goal of each of these therapies is to improve blood lipid and lipoprotein characteristics, beneficial effects on energy metabolism and cardiovascular function such as improved endothelial function, reduced oxidative stress, decreased platelet adhesion and increased atherosclerotic plaque stability may help to explain at least part of the cardioprotective benefits of these agents. Emerging evidence also suggests that certain classes of lipid-lowering drugs modulate the synthesis and secretion of adipose-tissue secreted proteins referred to as adipokines.

Although adipose tissue is a well-known storage depot for excess calories, its role as an endocrine organ was not appreciated until the discoveries of leptin and adiponectin in the mid-1990s. Since then, over 100 adipokines have been identified in adipose tissue. Several adipokines have been speculated or known to regulate energy homeostasis, metabolism and cardiovascular function. The purpose of this review is to present our current understanding of the capacity and potential mechanisms by which the most commonly used lipid-lowering drugs (statins, fibrates, niacin and omega-3 fatty acids) alter the synthesis and secretion of adipokines. A more thorough understanding of the capacity of lipid-lowering agents to alter the production and/or secretion of adipokines has the potential to improve our understanding of the metabolic pathways that regulate glucose and lipid metabolism and could lead to the development of potentially superior treatments in the future. Although not within the scope of this review, we acknowledge that the discovery and improved understanding of other un-intended targets besides adipokines may also be important for the cardioprotective effects of lipid-lowering drugs.

LEPTIN

The discovery of leptin in 1994 brought about an exciting era for the study of adipocyte-secreted proteins[7]. Leptin is produced in proportion to body fat stores and acts as an adiposity signal to the brain[8,9]. Intracerebroventricular or intraperitoneal administration of leptin attenuates the characteristic hyperphagic and hypometabolic phenotype of leptin deficient (ob/ob) mice[10]. Although leptin deficiency is rare in humans, obesity is associated with central and peripheral leptin resistance. Indeed, obesity impairs the leptin signaling cascade potentiating an increase in the production of leptin[11]. Leptin activates specific neurons within the arcuate nucleus of the hypothalamus which are associated with a reduction in the activation of neuropeptide-Y expressing neurons. In addition to promoting weight loss by altering feeding behavior and energy expenditure, leptin also possesses important effects on insulin-signaling and hepatic glucose production[12-14].

Statins inhibit HMG-CoA reductase, a key enzyme in the hepatic synthesis of cholesterol, and subsequently up-regulate hepatic LDL receptors. Patients with type 2 diabetes (T2DM) experience a cardioprotective effect from low dose atorvastatin therapy[15] and the magnitude of protection may be greater than what is seen in nondiabetic individuals[16]. This may be due to statin-induced reductions in elevated leptin levels seen in obesity and T2DM that do not occur in normal weight, nondiabetic individuals. Chronically elevated leptin concentrations may have effects on the cardiovascular system that are pro-atherogenic, pro-thrombotic and pro-angiogenic[17-19]. Therefore subjects with pathologically elevated leptin levels may experience an added benefit from statins.

In fact, 6 wk of atorvastatin treatment (2.5 mg/kg/d) in hypercholesterolemic rabbits reduced serum leptin concentrations by 37.7%[20]. Moreover, 8 wk of ator vastatin treatment (40 mg/d) in obese humans with T2DM reduced plasma leptin concentrations by 40%[16,20]. However, 12 wk of pravastatin treatment (40 mg/d) in humans with normal cholesterol concentrations had no effect on serum leptin concentrations (Table 1)[21]. These data support the notion that the additional benefits of statins on circulating leptin require a pathophysiological elevation in blood lipids or leptin. Contrary to the previous findings, one study found that neither 16 wk of atorvastatin nor pravastatin therapy had any effect on serum leptin concentrations in humans with hypercholesterolemia[22]. The results of this study may be explained by the study population which consisted mostly of lean subjects without T2DM and/or their use of a lower dose, (10 mg/d) of pravastatin or atorvastatin, while the other human studies used a dose of 40 mg/d. Although these subjects did not experience a reduction in plasma leptin concentrations, they did experience cardioprotective benefits from atorvastatin therapy including reduced total and LDL cholesterol and triglycerides and reduced circulating concentrations of the inflammatory markers high-sensitivity C-reactive protein and tumor necrosis factor-α (TNF-α)[22].

Taken together, it appears that obese non-diabetic and diabetic individuals with elevated circulating leptin concentrations may benefit from statin therapy more than

Table 1 Effects of statins on circulating adipokines

Subjects	Treatment	Effects on circulating adipokines	Ref.
Male New Zealand rabbits with hypercholesterolemia	6 wk of 2.5 mg/kg per day atorvastatin	Leptin decreased by 38% from 8.9 ± 2.3 to 5.5 ± 2.8 μg/mL ($P < 0.05$)	[20]
Humans with T2DM[a]	8 wk of 40 mg/d atorvastatin	HMW increased by 42.3% while MMW and LMW decreased by 21% and 23% respectively. Total adiponectin did not change. (2009 article) Leptin decreased by 40% from 20.7 ± 2.3 to 12.5 ± 1.1 ng/mL. Resistin decreased by 20% from 3.5 ± 0.4 to 2.9 ± 0.4 μg/mL	[95]
Healthy humans	12 wk of pravastatin (40 mg/d)	No changes in adiponectin or leptin	[21]
Humans with hypercholesterolemia	4 mo of pravastatin or atorvastatin (10 mg/d)	Adiponectin increased from 10.7 ± 4.7 to 11.0 ± 5.1 μg/mL in response to atorvastatin ($P < 0.05$). No change in leptin or resistin. Atorvastatin reduced TNF-α from 2.0 ± 1.0 to 1.7 ± 0.6 ($P < 0.05$)	[22]
Humans with hyperlipidemia	6 mo of simvastatin (10 mg/d) or pitavastatin (2 mg/d)	Adiponectin increased in response to pitavastatin but not in response to simvastatin	[74]
Humans with increased cardiovascular risk	12 wk of 10-80 mg/d atorvastatin	Adiponectin increased by 10% with maximal increase (25%) observed at 80 mg/d ($P < 0.05$)	[75]
Humans with hypercholesterolemia and CAD[b]	6 mo of 10-20 mg/d pravastatin	Adiponectin increased by 16.8% from 7.2 to 7.8 μg/mL ($P < 0.001$)	[76]
Humans with hypercholesterolemia and ischemic heart disease	3 mo of 10 mg/d atorvastatin	Adiponectin increased from 9.7 ± 7.4 to 13.9 ± 9.98 μg/mL ($P < 0.005$)	[77]
C57BL/6J mice	0-15 wk of 0.06% of diet as pravastatin	Adiponectin increased ($P < 0.01$)	[78]
Men with hypercholesterolemia	1 year of 40 mg/d pravastatin	Adiponectin increased by 1.47 ± 0.33 μg/mL ($P < 0.05$)	[78]
Humans with CAD[b] and IGT[c]	6 mo of 20 mg/d pravastatin	Adiponectin increased by 35% from 5.2 to 6.1 μg/mL ($P < 0.001$)	[79]
Humans with stable CAD[b], hypercholesterolemia and hypertriglyceridemia	6 mo of 10 mg/d atorvastatin	Adiponectin increased by 4 wk ($P < 0.05$), with further increases by 6 mo ($P < 0.01$). Atorvastatin decreased TNF-α ($P < 0.01$)	[80]
Humans with MetS	40 mg/d simvastatin for 8 wk	No change in adiponectin	[81]
Humans at cardiovascular risk	3 mo of 40 mg simvastatin	Adiponectin decreased from 15.5 ± 12.7 to 11.6 ± 7.0 μg/mL ($P < 0.05$)	[82]
Nondiabetic humans with increased cardiovascular risk	3 mo of simvastatin (40 mg/d)	Adiponectin decreased. No change in RBP4	[83]
Humans with hypercholesterolemia	2 mo of 10-80 mg/d simvastatin	Adiponectin decreased with maximal decrease (10%) observed at 80 mg/d ($P < 0.05$)	[84]
Humans with hypercholesterolemia	2 mo of simvastatin (20 mg/d) or pravastatin (40 mg/d)	Simvastatin decreased adiponectin (5.8 ± 0.8 to 5.2 ± 0.6 μg/mL); pravastatin increased adiponectin (5.6 ± 0.6 to 6.1 ± 0.6 μg/mL)	[85]
Humans with hypercholesterolemia on fluvastatin plus TLC[e] and 19 humans with normal cholesterol on TLC alone	12 wk of 80 mg/d fluvastatin plus TLC ($n = 24$) or 12 wk of TLC alone ($n = 19$)	Adiponectin increased from 5.3 ± 1.5 to 6.2 ± 2.2 μg/mL in response to TLC ($P < 0.05$), but was unchanged in response to fluvastatin	[91]
Humans with T2DM[a] and mixed hyperlipoproteinemia	6 wk of 10 mg/d atorvastatin	No change in adiponectin or resistin	[92]
Kidney transplant recipients	12 wk of atorvastatin (10 mg/d)	No change in adiponectin or TNF-α	[93]
Humans with T2DM or at high risk for T2DM	12 wk of atorvastatin (20 mg/d)	No effect on adiponectin, resistin or TNF-α	[94]
Humans with T2DM[a]	6 mo of 10 mg/d atorvastatin	Resistin tended to decrease, although not significant ($P = 0.11$)	[131]

[a]Type 2 diabetes mellitus; [b]Coronary artery disease; [c]Impaired glucose tolerance; [d]Lipopolysaccharide; [e]Therapeutic lifestyle changes. TNF-α: Tumor necrosis-factor-α; RBP4: Retinol binding protein 4; HMW: High-molecular weight; LMW: Low-molecular weight; MMW: Middle-molecular weight; T2DM: Type 2 diabetes; Ref: Reference.

lean individuals with lower plasma leptin concentrations. It is difficult to make a definitive conclusion as few studies have examined the effects of statins on serum leptin levels in healthy subjects.

Fibrates lower triglycerides by limiting substrate availability for triglyceride synthesis in the liver[23,24], promoting the action of lipoprotein lipase[25,26], enhancing LDL receptor/ligand interaction[27], promoting cholesterol excretion *via* bile[28] and stimulating reverse cholesterol transport[29]. The ultimate result is a reduction in triglyceride and LDL-C levels, but the data on HDL-C are varied.

In addition to improving blood lipids, fibrate therapy often results in an improvement in insulin sensitivity. The mechanisms by which fibrates improve insulin sensitivity are unclear, yet studies suggest that fibrates bind to the nuclear receptor, PPARα, and may improve insulin sensitivity by increasing hepatic fatty acid oxidation[30,31]. Another mechanism may be through regulation of expression of adipokines involved in insulin sensitivity like adiponectin, leptin, TNF-α, retinol binding protein 4 (RBP40 and resistin.

Fibrate therapy appears to reduce high-fat diet-induced increases in circulating leptin levels. In Wistar rats treated with gemfibrozil (75 mg/kg per day) for 28 d, a significant decrease in serum leptin concentrations was observed in rats on a high-fat diet ($P < 0.01$), but not on a standard

chow diet[32]. Another study found that fenofibrate reduced plasma leptin concentrations and leptin mRNA levels in epididymal adipose tissue of rats on a high-fat diet and not in those on a standard chow diet[33]. Furthermore, clofibrate administration had no effect on leptin mRNA levels in white and brown adipose tissue in rats on a standard diet[34]. It is possible that fibrate's ability to alter plasma leptin concentrations is dependent on the metabolic state of the animal, i.e. fibrates actions on leptin may be more effective if leptin is elevated due to poor diet and/or obesity.

Damci *et al*[35] treated obese patients with T2DM and hypertriglyceridemia with fenofibrate (250 mg/d) for 3 mo. Not surprisingly, these patients also had elevated serum leptin levels. Consistent with previous findings, after 3 months of fenofibrate treatment, serum leptin levels were significantly reduced from 266 ± 205 to 157 ± 122 pg/mL. The authors noted that since elevated leptin levels are associated with insulin resistance and CVD, this reduction in serum leptin concentrations is a beneficial added effect of fenofibrate therapy[35]. On the other hand, Belfort and colleagues examined the effects of fenofibrate in obese non-diabetic insulin-resistant subjects with metabolic syndrome[36]. They found that after 12 wk of fenofibrate therapy (200 mg/d), plasma leptin levels were unchanged.

Altschul *et al*[37] showed in 1955 that nicotinic acid (niacin) lowered plasma cholesterol in normal and hypercholesterolemic subjects. Since then, niacin has been used in pharmacologic doses as a lipid-lowering drug. Niacin is the most effective pharmacological agent for increasing HDL-C and also lowers triglycerides and to a lesser extent LDL-C[38]. The effects of niacin on circulating leptin concentrations are controversial. We observed that an acute dose of niacin (30 mg/kg) given to male Sprague-Dawley rats produced no change in serum leptin levels[39]. In addition, a chronic study in humans examined the effects of four and six weeks of extended-release niacin (1000 mg and 1500 mg respectively) on circulating leptin[40]. During both treatment durations, serum leptin concentrations were unchanged[40]. However, when niacin (200 mg/kg per day for 6 wk) was administered to hypercholesterolemic rabbits, serum leptin concentrations decreased by 22%[41]. Yet, data collected from two separate human studies support the notion that niacin actually increases circulating leptin concentrations[42,43]. These studies were conducted in humans with either metabolic syndrome or T2DM. Westphal *et al*[44] found that six weeks of extended-release niacin (1500 mg/d) resulted in a 27% increase in serum leptin concentrations in men with the metabolic syndrome. In addition, a small study examined the effects of acipimox, a nicotinic acid analogue, in humans with T2DM. They found that circulating leptin levels were significantly increased by 3 d of acipimox (125 mg every 2 h)[43].

A primary naturally occurring source of omega-3 fatty acids are deep-water fish, however fish oil supplements are also frequently used to obtain higher intakes of omega-3 fatty acids. Important nutritional omega-3 fatty acids are α-linolenic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Since consumption of omega-3 fatty acids has been associated with reduced CVD risk, recommendations commonly include the intake of 1 gr am/d of EPA and DHA[45,46]. The greatest benefit of omega-3 fatty acids is a reduction of triglyceride levels in people with hypertriglyceridemia[47]. Omega-3 fatty acids have also been shown to reduce very low-density lipoprotein cholesterol and LDL-C levels, as well as mildly increase HDL-C[48,49]. While the triglyceride-lowering effect of omega-3 fatty acids is widely accepted and omega-3 fatty acids are generally thought of as beneficial to cardiovascular health, the effects of these fatty acids on LDL-C and HDL-C are varied. Omega-3 fatty acids can increase LDL-C levels in hypertriglyceridemic patients and studies have shown little or no effect of omega-3 fatty acids on HDL-C[49]. In addition, omega-3 fatty acids have been found to alter adipokine profile.

Under cell culture conditions, the effects of omega-3 fatty acids on leptin are varied. Murata *et al*[50] reported in 2001 that EPA increases leptin mRNA expression and secretion in 3T3-L1 adipocytes. However in the same year, Reseland *et al*[51] demonstrated that EPA and DHA reduce leptin mRNA expression in 3T3-L1 adipocytes.

Peyron-Caso and colleagues reported that omega-3 fatty acids upregulate plasma leptin levels in insulin-resistant rats by 70% after three weeks of fish oil and 75% after six weeks[52]. Subsequently, an affiliated group demonstrated that omega-3 fatty acids were able to reverse the inhibitory effect of a long-term sucrose-rich diet on serum leptin levels in insulin-resistant rats[53]. Another group has demonstrated that supplementing a high-fat diet with the omega-3 fatty acid EPA, results in both increased plasma leptin concentrations and gene expression in epididymal white adipose tissue, while supplementation of a standard diet with EPA significantly lowered leptin levels and gene expression[54].

Sneddon and colleagues examined whether conjugated linoleic acid (CLA) and omega-3 fatty acids would affect circulating adipokines in young or old lean and obese men. They found no effects of CLA plus EPA/DHA on plasma leptin levels in any of the groups[55]. Other studies have also found that plasma leptin concentrations are unchanged in response to omega-3 fatty acids[56]. As the results of these studies are conflicting, further investigations into the effects of omega-3 fatty acids on leptin are needed.

ADIPONECTIN

Adiponectin is one of the most abundantly secreted proteins in the body, accounting for up to 0.05% of total plasma proteins[57]. Adiponectin is expressed as a 30 kDa monomer and undergoes posttranslational modification to form higher order structures including: (1) homotrimers of 90 kDa; (2) hexamers of 180 kDa (low-molecular weight); and (3) 12-18 mers of greater than

300 kDa [high-molecular weight (HMW)][58]. The HMW multimer is an active form of adiponectin and its ratio to total adiponectin is correlated with insulin sensitivity (SA ratio)[59-61]. Adiponectin is constitutively expressed in adipose tissue and its expression is reduced in the presence of obesity[62]. Adiponectin possesses important effects on insulin sensitivity, intermediary metabolism and vascular inflammation[63-66]. Adiponectin decreases insulin resistance by decreasing the triglyceride content in the muscle and liver of obese mice[67] and enhancing hepatic insulin sensitivity[68]. During fasting, adiponectin enhances AMPK activity in the arcuate nucleus of the hypothalamus *via* activation of its receptor, AdipoR1, stimulates food intake, and decreases energy expenditure[69]. Adiponectin also directly improves endothelial dysfunction by stimulating production of nitric oxide[70], inhibiting proliferation of vascular smooth muscle cells[71,72], and inhibiting the conversion of macrophages to foam cells[73].

Evidence suggests that serum adiponectin concentrations increase in response to atorvastatin, pitavastatin and pravastatin (Table 1)[22,74-80]. Indeed, atorvastatin increased plasma adiponectin levels in men with hypercholesterolemia and increased adiponectin production and secretion in 3T3-L1 adipocytes[78]. Conversely, other studies examining the effects of simvastatin demonstrated that adiponectin concentrations were either unchanged[74,81] or reduced[82-85]. Nomura and colleagues tested the effects of either pitavastatin or simvastatin in humans with hypercholesterolemia and found that plasma total adiponectin concentrations increased after six months of pitavastatin treatment, but were unaffected by simvastatin[74]. Koh *et al*[85] compared pravastatin therapy to simvastatin therapy in hypercholesterolemic patients and found that pravastatin increased while simvastatin decreased plasma adiponectin concentrations.

Additional studies utilizing simvastatin[74], pravastatin[21], fluvastatin[91] or atorvastatin[92-94] in a variety of subjects (healthy humans, humans with hypercholesterolemia or hyperlipoproteinemia or kidney transplant recipients) all found no change in circulating adiponectin concentrations in response to statin treatment. A possible explanation for this discrepancy may involve the analysis of the different multimers of adiponectin. One study conducted in humans with T2DM found no change in total adiponectin in response to atorvastatin, but observed a 42% increase in the biologically active HMW adiponectin and a 21% and 23% decrease in the middle- and low- molecular weight forms of adiponectin, respectively, in response to 8 wk of atorvastatin[95]. A more recent study also demonstrated that simvastatin caused a 40% reduction in the HMW form of adiponectin, whereas total adiponectin levels remained unchanged[96]. Thus, simvastatin caused a redistribution of complexes resulting in a reduction in circulating HMW adiponectin and an increase in the low-molecular weight form of adiponectin resulting in a zero-sum gain[96].

The singular and inconsistent effects of simvastatin on circulating adiponectin may be linked to pharmacokinetic differences within the statin class. It is well known that the hepatoselectivity of statins is related to their lipophilicity in the sense that lipophilic statins are less hepatoselective and achieve higher levels of exposure in non-hepatic tissues[89,90]. Simvastatin is the most lipophilic within this class and may cause undesirable effects such as reductions in post-prandial insulin secretion and exacerbation of insulin resistance[85-88]. On the other hand, pravastatin, the most hydrophilic, may cause favorable effects such as improvement in insulin sensitivity[79]. It is tempting to speculate that the simvastatin-mediated reduction in circulating insulin and/or peripheral insulin resistance reduces signaling input through an unknown pathway that regulates the maturation and secretion of the HMW forms of adiponectin. Overall, the results of these studies suggest that the more hydrophilic statins may increase circulating adiponectin concentrations; however, a careful examination of the adiponectin multimers should be conducted to enhance interpretation in future studies.

Both fenofibrate and bezafibrate have been shown to increase adiponectin gene expression and circulating adiponectin concentrations. Adiponectin mRNA levels measured in epididymal fat isolated from rats on a high-fat, high-glucose diet also increased as a result of fenofibrate treatment (Table 2)[33]. Five separate studies showed increases in total circulating adiponectin (Table 2)[80,97-100] with fibrate therapy and one showed an increase in HMW adiponectin, but not total[101]. Additional studies also showed no change in total adiponectin but did not measure changes in HMW adiponectin following fibrate therapy[33,92,102]. An analysis of the different adiponectin complexes should be implemented in future studies to fully assess the impact of fibrates on adiponectin levels since an increase in HMW adiponectin even in the absence of changes in total adiponecti would be expected to impart health-related benefits. Future studies will be required to identify the precise mechanisms by which fibrates increase adiponectin mRNA and protein expression and how these effects differ from other agents such as statins which appear to have post-translational effects on adiponectin secretion.

While the effects of niacin on leptin remain unresolved, the effects of niacin on circulating adiponectin concentrations are robust and consistent. Each study that has examined the response of adiponectin to niacin administration has found that adiponectin increases as a result of niacin treatment (Table 3)[39,40,44,103,104]. Westphal and colleagues reported that serum total adiponectin concentrations increased by 54% in humans after four weeks of extended-release niacin (1000 mg/d) and by 94% after 6 wk (1500 mg/d) in patients with cardiovascular disease[40]. An additional study conducted by the same group reported that 6 wk of extended-release niacin (1500 mg/d) increased serum total adiponectin concentrations by 56% in men with the metabolic syndrome[44]. Since the HMW complex is the most biologically active form of adiponectin[60], independent studies conducted by Westphal and colleagues and our group were conducted in

Table 2 Effects of fibrates on circulating adipokines

Subjects	Treatment	Effects on circulating adipokines	Ref.
Male Wistar rats on standard diet or HFD[d]	28 d of 75 mg/kg per day gemfibrozil	Leptin decreased in rats on HFD[d] ($P < 0.01$). No change in leptin in rats on standard diet.	[32]
Wistar rats on high-fat, high-glucose diet	8 wk of fenofibrate (50 mg/kg/d)	Fenofibrate reduced plasma leptin levels; no effect on plasma adiponectin. Fenofibrate reduced leptin mRNA levels; and increased adiponectin mRNA levels in epididymal fat	[33]
Rats	14 d of clofibrate	No effect on leptin mRNA levels in brown or white adipose tissue	[34]
Obese humans with T2DM and hypertriglycer-idemia	3 mo of fenofibrate (250 mg/d)	Serum leptin levels decreased from 266 ± 205 to 157 ± 122 pg/mL ($P = 0.003$)	[35]
Humans with hypertriglycer-idemia, central obesity, other characteristics of MetS	12 wk of fenofibrate (160 mg/d)	Adiponectin increased 7.7% from 4.10 to 4.50 μg/mL	[97]
Humans with stable CAD[b], hypercholester-olemia and hypertriglyceridemia	6 mo of bezafibrate (400 mg/d)	Adiponectin increased by 4 wk ($P < 0.05$), with further increases by 6 mo ($P < 0.01$). Bezafibrate reduced TNF-α	[80]
Nondiabetic men with insulin resistance and dyslipidemia; Male sprague-dawley rats on HFD; 3T3-L1 adipocytes	8 wk of fenofibrate (200 mg/d) in humans. 2 wk of fenofibrate (200 mg/kg per day) in rats. 24 h of fenofibrate (10, 50, 100 μmol/L) in 3T3-L1 adipocytes.	Fenofibrate decreased serum RBP4 (34.8 ± 4.0 to 24.4 ± 2.1 μg/mL) and increased adiponectin (11.3 ± 6.7 to 16.5 ± 7.2 μg/mL) in humans. Fenofibrate reduced the HFD-induced increase in RBP4 in rats. Fenofibrate reduced HFD-induced increase in RBP4 mRNA in adipose tissue of rats. Fenofibrate attenuated the HFD-induced decrease in adiponectin mRNA in adipose tissue of rats. Fenofibrate suppressed RBP4 mRNA levels by 22% at highest concentration and increased adiponectin mRNA levels by 46% at highest concentration in 3T3-L1 adipocytes	[100]
Humans with MetS[c]	Longitudinal study over a period of ~6.2 year of 400 mg/d bezafibrate	After 2 year of treatment, adiponectin increased, with the median percentage change being +9.8% ($P < 0.0001$)	[98]
Humans with hypertriglyceridemia; some with MetS[c]	8 wk of fenofibrate (200 mg/d)	Adiponectin increased by 14% ± 5% ($P = 0.008$)	[99]
Men with hypertriglyceridemia	12 wk of 150 mg/d ($n = 7$) or 4 wk of 150 mg/d then 8 wk of 300 mg/d ($n = 4$) fenofibrate	HMW[b] adiponectin increased from 3.0 ± 1.5 to 3.4 ± 1.7 μg/mL ($P < 0.05$). No change in total adiponectin	[101]
Humans with T2DM[a] and mixed hyperlipoproteinemia	6 wk of fenofibrate (200 mg/d)	No change in adiponectin or resistin	[92]
Humans with insulin-resistant MetS[c]	12 wk of fenofibrate (200 mg/d)	No change in plasma leptin, adiponectin or TNF-α concentrations	[36]
Obese women with T2DM[a]	3 mo of fenofibrate (200 mg/d)	No effect on adiponectin or resistin	[102]
Hypercholesterolemic rabbits and adipocytes from these rabbits	4 wk of fenofibrate (30 mg/kg per day or 10-100 μmol/L)	Fenofibrate decreased high cholesterol diet-induced increases in TNF-α by 44.7%. Fenofibrate reduced TNF-α release by adipocytes ($P < 0.05$) compared to the high cholesterol group (10.45 ± 0.33 *vs* 17.23 ± 0.26 pg/mL, $P < 0.05$)	[123]

[a]Type 2 diabetes mellitus; [b]High molecular weight; [c]Metabolic syndrome; [d]High-fat diet. TNF-α: Tumor necrosis-factor-α; RBP4: Retinol binding protein 4; HMW: High-molecular weight; T2DM: Type 2 diabetes; Ref: Reference.

individuals with metabolic syndrome to determine which form(s) of adiponectin is targeted by niacin.[103,104]. Niacin increased serum low- and medium-molecular weight adiponectin, but preferentially increased the circulating concentrations of the HMW multimer in both studies. Additional studies from our group demonstrate that niacin increases adiponectin secretion in primary rat adipocytes and 3T3-L1 adipocytes stably expressing the niacin receptor in a receptor-dependent fashion[39]. We have also shown that a single dose of immediate-release niacin (30 mg/kg) acutely elevates serum adiponectin concentrations in rats and mice expressing the niacin receptor but not in mice with a genetic deletion of the receptor[39]. Taken together, these studies suggest that both immediate and extended-release formulations of niacin increase serum total and HMW adiponectin concentrations and that these effects may occur rapidly following a single dose of niacin at least in rodents.

Omega-3 fatty acids have also shown potential as a strategy to raise adiponectin concentrations[53]. Rossi *et al* conducted a study to evaluate the long-term regulation of leptin and adiponectin by dietary fish oil in insulin-resistant rats. They established that dietary fish oil reversed the inhibitory effects of a long-term sucrose-rich diet on serum leptin and total adiponectin levels[53]. Since then, many studies have confirmed that dietary fish oils and omega-3 fatty acids increase total adiponectin concentrations[54,56,105-108].

Sneddon and colleagues examined the effects of CLA and omega-3 fatty acids on plasma leptin and adiponectin concentrations[55]. While there was no effect on leptin, they demonstrated that plasma adiponectin concentrations increased by 12% with CLA plus EPA/DHA in young, obese subjects, but no change was observed in the older obese subjects or in the treated lean subjects[55]. Other studies with omega-3 fatty acids have observed no effect

Table 3 Effects of niacin on circulating adipokines

Subjects	Treatment	Effects on circulating adipokines	Ref.
Male sprague-dawley rats	Acute dose of 30 mg/kg niacin (n = 6)	Adiponectin increased by 37% at 10 min, peaked at 1 h and remained elevated for 24 h (P < 0.05). No change in resistin or leptin	[39]
Male New Zealand rabbits on high-cholesterol diet	6 wk of 200 mg/kg per day niacin (n = 6)	Leptin decreased by 22% from 6.87 ± 1.58 to 8.79 ± 1.45 ng/mL (P < 0.05)	[41]
Men with MetS[a]	6 wk of 1500 mg extended-release niacin	Adiponectin increased by 46% from 5.7 ± 0.5 to 8.4 ± 0.7 μg/mL (P < 0.05)	[104]
Men with MetS[a]	6 wk of 1500 mg extended-release niacin	Adiponectin increased by 56% from 6.1 ± 2.3 to 10.1 ± 4.0 μg/mL (P < 0.01). Leptin increased by 27% from 19.8 ± 21.4 to 24.6 ± 26.8 ng/mL (P < 0.05). No change in resistin, TNF-α, IL-6	[42]
Men with MetS[a]	6 wk of 1500 mg extended-release niacin	Low- and medium-molecular weight adiponectin increased by 35% and 33%, respectively, but HMW adiponectin by 88% (all P < 0.05)	[103]
Humans	6 wk of 1500 mg extended-release niacin	Adiponectin increased by 94% from 4.83 ± 2.39 to 9.35 ± 6.06 μg/mL (P < 0.01). No change leptin or resistin	[40]
Humans	4 wk of 1000 mg extended-release niacin	Adiponectin increased by 54% from 4.83 ± 2.39 to 7.45 ± 5.71 μg/mL (P < 0.01). No change in leptin. Resistin decreased by 8.3% from 3.97 ± 2.25 to 3.64 ng/mL (P < 0.05)	[40]
Humans with T2DM[b]	3 d of 125 mg acipimox every 2 h	Leptin increased by 2.38 ± 0.57 ng/mL (P < 0.005)	[43]

[a]Metabolic syndrome; [b]Type 2 diabetes mellitus. TNF-α: Tumor necrosis-factor-α; HMW: High-molecular weight; T2DM: Type 2 diabetes; Ref: Reference.

on plasma total or HMW adiponectin levels[109], while still others have demonstrated that in cell culture conditions, EPA actually reduces adiponectin gene expression and secretion[110]. The authors attributed this to reduced PPARγ mRNA levels which resulted from EPA treatment. PPARγ activation stimulates adiponectin gene expression and secretion[111]. Therefore, the reduction in adiponectin gene expression, synthesis and secretion in the presence of EPA, which increases fatty acid oxidation, may be a decompensatory mechanism in adipose tissue since omega-3 fatty acids are working directly on the liver and adiponectin increases fatty acid oxidation in liver[112].

TNF-α

TNF (or cachectin) was discovered in 1975 as a "substance released by the host indirectly in response to endotoxin which results in the hemorrhagic necrosis of tumors" [113]. TNF-α is a proinflammatory cytokine produced and secreted by many tissues, primarily macrophages, but is also produced by adipocytes[114]. TNF-α is constitutively expressed in adipose tissue and adipose tissue expression is elevated in obesity[115]. TNF-α exerts many of its effects by binding to either a 55 kDa cell membrane receptor, TNFR-1 or a 75 kDa cell membrane receptor, TNFR-2[116-119]. Some studies indicate that TNFR-1 mediates apoptosis and TNFR-2 mediates proliferation, while others propose that the receptors signal as one[120-122]. TNF-α serves as a marker for inflammation and is associated with increased risk for coronary artery disease and insulin resistance. Therefore, its response to lipid-lowering drugs is intriguing.

Ando and colleagues demonstrated that atorvastatin (10 mg/d for 4 mo) significantly reduced the concentration of TNF-α in 36 hypercholesterolemic men compared with pravastatin treatment[22]. Nakamura *et al*[80] also found that six months of atorvastatin therapy reduced TNF-α concentrations in patients with hypercholesterolemia and hypertriglyceridemia. These two studies suggest that atorvastatin has beneficial effects to lower this proinflammatory cytokine. However, a similar twelve-week study conducted in kidney transplant recipients demonstrated that atorvastatin treatment does not affect TNF-α levels[93]. Furthermore, another 12 wk study found that atorvastatin does not affect TNF-α concentrations in humans with or at high risk of developing diabetes[94]. These findings suggest that correcting the underlying dyslipidemia may have a direct role in lowering TNF-α concentrations.

Zhao *et al*[123] examined the effects of fenofibrate treatment on serum TNF-α concentrations in hypercholesterolemic rabbits and on adipocyte secretion of TNF-α. Fenofibrate treatment decreased high cholesterol diet-induced elevations in serum TNF-α concentrations in hypercholesterolemic rabbits by nearly 45%. In addition, fenofibrate (10 to 100 μmol/L) greatly reduced TNF-α secretion from adipocytes of hypercholesterolemic rabbits[123]. Nakamura and colleagues found that bezafibrate therapy also reduced levels of TNF-α in patients with hypercholesterolemia and hypertriglyceridemia[80]. Taken together, fibrate therapy appears to be extremely advantageous regarding its ability to reduce TNF-α concentrations.

Few studies have measured circulating TNF-α levels after niacin treatment. Two separate studies in men with metabolic syndrome measured the effects of six weeks of niacin (1500 mg/d) on circulating adipokines and found no change in TNF-α levels[44,124]. Although these results suggest niacin does not affect TNF-α concentrations, more studies are needed to conclusively determine the effects of niacin on TNF-α.

Rats fed a fat-rich, hyperenergetic diet had significantly increased TNF-α gene expression. When another group of rats were fed the same diet supplemented with EPA, the rise in TNF-α expression was prevented[54]. In addition, a dietary supplementation of fish oil, rich

in EPA and DHA, significantly lowered plasma TNF-α concentrations when given to the normoglycemic offspring (age 29.9 ± 6.2 years) of patients with T2DM[125]. Taken together, although the studies are few, omega-3 fatty acids appear to have positive effects on TNF-α levels.

RETINOL BINDING PROTEIN 4

RBP4 is primarily derived from the liver, with adipose tissue contributing approximately 20% of circulating RBP4. Elevated RBP4 concentrations contribute significantly to the insulin resistance observed in obesity and type 2 diabetes in both rodents and humans[126,127]. Lowering of serum RBP4 concentrations by treatment with fenretinide, a synthetic retinoid which promotes RBP4 excretion, results in normalization of serum RBP4 levels and improvements in insulin resistance in obese mice[127]. In humans, RBP4 appears to be a good biomarker for insulin resistance and the metabolic syndrome, but the regulation of RBP4 is unclear.

Very little is known regarding the impact of statins on RBP4 concentrations. One study examined the effect of simvastatin (40 mg for 3 mo) on RBP4 plasma concentrations in nondiabetic patients with metabolic syndrome at increased risk for cardiovascular complications[83]. In this study, circulating RBP4 levels were unchanged in response to simvastatin treatment[83].

Since fibrates have been shown to both improve insulin resistance and influence levels of circulating adipokines, one mechanism by which fibrates could increase insulin sensitivity may be through a reduction in circulating RBP4. Wu and colleagues examined the effects of fenofibrate treatment in 3T3-L1 adipocytes, rats and humans[128]. Fenofibrate treatment reduced the mRNA expression levels of RPB4 in 3T3-L1 adipocytes[128]. Furthermore, fenofibrate significantly decreased RBP4 mRNA levels in adipose tissue but not in the liver of obese rats, which correlated with decreased serum RBP4 concentrations and increased insulin sensitivity[128]. In addition, in men with insulin resistance and dyslipidemia, 8 wk of fenofibrate treatment resulted in a 30% reduction in serum RBP4 concentrations which correlated with reduced body weight and increased insulin sensitivity[128]. These results suggest that fenofibrate may improve insulin sensitivity through a reduction in serum RBP4 concentrations.

RESISTIN

Adipose-tissue derived resistin has been implicated in the development of insulin resistance in rodents[129]. However, the precise function of resistin in humans is unclear. Human resistin is expressed primarily by macrophages and appears to be involved in the recruitment of other immune cells and the secretion of pro-inflammatory factors[130]. Human resistin may contribute to type 2 diabetes by interfering with insulin signaling and may be involved in the development of atherosclerosis by promoting the formation of foam cells[130].

Studies on resistin's response to statin therapy are somewhat controversial. In the majority of studies, atorvastatin therapy in humans with T2DM or hypercholesterolemia resulted in no change in circulating resistin concentrations[22,92,94,131]. Yet, one study in patients with T2DM found that 8 wk of atorvastatin therapy lowered resistin concentrations by 20%[16]. The results of this study may be different than others due to their use of a two- to four-fold higher dose of atorvastatin compared to many of the other studies (40 mg/d compared to 10 or 20 mg/d). The investigators also note that Shetty *et al*, one of the groups that found no significant effect of atorvastatin on resistin levels, observed a similar decrease in resistin levels in the placebo group as the atorvastatin-treated group, likely due to chance[94]. So in fact, resistin levels decreased significantly after atorvastatin treatment, but it decreased to the same extent in the placebo group, indicating that atorvastatin had no effect on resistin concentrations. Shetty *et al*[94] found similar results even after diabetic and nondiabetic subjects were considered separately. Furthermore, another study noted that although not significant, resistin tended to decrease after 6 mo of atorvastatin treatment (10 mg/d) in humans with T2DM ($P = 0.11$)[131]. All together, it can be concluded that statin therapy has little to no effect on circulating resistin.

The small body of literature on the effects of fibrates on resistin suggests there are no effects. Two studies examining the effect of fenofibrate (200 mg/d for 6 wk in one study and 3 mo in the other) on circulating resistin concentrations found that fenofibrate did not change resistin concentrations in humans with T2DM[92].

Most studies that have measured resistin levels after niacin treatment have observed no change in resistin concentrations[39,40,44]. We demonstrated that treating primary rat adipocytes and 3T3-L1 adipocytes stably expressing the niacin receptor with niacin resulted in no change in resistin secretion into the media[39]. We also recently reported that a single dose of niacin (30 mg/kg), while acutely elevating serum adiponectin concentrations, had no effect on resistin levels in rats or mice[39]. Westphal and colleagues measured circulating resistin levels in humans after four and 6 wk of niacin treatment. After 4 wk they found that resistin significantly decreased by 8.3% from baseline, but after 6 wk of treatment, resistin levels were not different from baseline[40].

CONCLUSION

With the increased occurrence of obesity comes a greater incidence of cardiovascular and metabolic diseases, often accompanied by hyperlipidemia. The use of lipid-lowering drugs is critical in the treatment of hyperlipidemia, but may also be affecting circulating adipokines in ways that could benefit or impair health. Although further studies will be required, the literature suggests that statins either have no effect on or decrease leptin concentrations, while

fibrates may reduce high-fat diet-induced increases in leptin concentrations. The effects of niacin on leptin are unclear as different studies have demonstrated that niacin has varying effects on circulating leptin levels. In addition, the data regarding the effects of omega-3 fatty acids on leptin are too varied to make a decisive conclusion about their effects.

High circulating adiponectin levels are known to have many protective effects including anti-diabetic, anti-atherosclerotic and anti-cancer properties. In addition to the improvement in blood lipid profile seen with these lipid-lowering therapies, the majority also beneficially increase circulating adiponectin concentrations. With the exception of simvastatin, statins increase total and HMW adiponectin, as do fibrates. Fibrates increase adiponectin concentrations, gene expression and secretion. Niacin has also conclusively been shown to increase circulating adiponectin concentrations (primarily the biologically active HMW multimer) both acutely and chronically. Omega-3 fatty acids have proven to be effective in the reduction of triglyceride and cholesterol levels. In addition to their favorable effect on blood lipids, they also increase circulating adiponectin levels. These results suggest that pharmacological reductions in blood lipids and adiponectin are associated. Future studies will be required to evaluate whether the reduction in blood lipids increase adiponectin or if the direct effects of pharmacological agents on serum adiponectin concentrations enhance their lipid-lowering capacity.

The few studies that have examined the effects of statins on TNF-α demonstrate that statins either have no effect on or reduce circulating TNF-α concentrations. ibrate therapy also reduces the high-cholesterol diet-induced increases in TNF-α concentrations. Further studies are needed to make a clear determination on the effects of niacin and omega-3 fatty acids on TNF-α.

Fibrate therapy reduces high-fat diet-induced increases in circulating RBP4 concentrations and gene expression. In addition, fibrate therapy also improves insulin sensitivity, possibly through a reduction in RBP4. Although one study examined the effects of statins on RBP4 and found no change, further studies are needed to establish the outcomes of statins, niacin, and omega-3 fatty acids on RBP4.

Adipose-tissue derived resistin has been implicated in the development of insulin resistance in rodents. However the precise function and regulation of resistin in humans is unclear. Unfortunately, the regulation of resistin by lipid-lowering drugs will remain unclear until further studies are completed. The majority of studies examining the effects of statins on resistin found that statins had no effect on resistin levels, although a few studies reported a slight reduction in circulating resistin, or a trend toward reduction, although not significant. In addition, the small body of literature on the effects of fibrates or niacin on resistin also suggests there is no effect.

Some of the protective effects of lipid-lowering drugs may be explained by the modulation of the synthesis and secretion of adipokines. However, more studies are needed to fully evaluate the effects of some classes of lipid-lowering drugs on adipokines. Furthermore, other effects of these drugs (in addition to their effects on adipokines) might share in some of the explanation into the supplementary health benefits observed aside from the reduction in blood lipids.

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