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REVIEW

EFFECT OF 3-HYDROXY-3-METHYLGLUTARYLCOENZYME A REDUCTASE INHIBITORS (STATINS) ON ADIPOSE TISSUE

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Abstract

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, a rate-limiting enzyme in cholesterol synthesis. Statins are widely used in the treatment of hypercholesterolemia and to reduce risk of acute cardiovascular and cerebrovascular events. Statins inhibit synthesis of not only cholesterol but also of non-steroid isoprenoids such as farnesyl- and geranylgeranylpyrophosphate, coenzyme Q (ubiquinone), dolichol, etc., which are involved in multiple cell metabolic and signaling cascades. Adipose tissue may be an important target for statins. Although statins have no effect on body weight and energy balance, they inhibit differentiation of preadipocytes to mature adipocytes and may induce adipocyte apoptosis. Stimulation of lipoprotein lipase in adipose tissue accelerates VLDL metabolism and may contribute to triglyceride-lowering effect of statins. According to some studies, statins reduce insulin sensitivity of adipose tissue and impair glucose metabolism in adipocytes. Statins also inhibit adipose tissue inflammation which plays an important role in obesity-associated pathologies. Finally, statins modulate production of adipokines such as leptin, adiponectin, resistin and visfatin. Currently available data suggest that effects on adipose tissue contribute to both beneficial and adverse consequences of statin therapy.

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Introduction

Statins are competitive inhibitors of 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase, a rate limiting enzyme in cholesterol biosynthesis, which converts HMG-CoA to mevalonate (Fig. 1). Currently available statins may be classified into two groups. Natural statins include lovastatin, which is a fungal metabolite, and its synthetic derivatives, pravastatin and simvastatin. Fluvastatin, atorvastatin and rosuvastatin are fully synthetic compounds with completely different chemical structure. Another synthetic statin, cerivastatin, was withdrawn from the market in 2001 due to many reported cases of fatal rhabdomyolysis. A new synthetic statin, pitavastatin, was introduced in 2003, however, until now is available only in Japan and India.

Statins decrease plasma low-density lipoprotein (LDL) cholesterol by inducing intracellular cholesterol depletion and upregulating hepatic LDL receptors. In addition, statins moderately increase HDL-cholesterol and reduce plasma triglycerides. Many clinical trials have demonstrated that statins effectively prevent acute cardi-

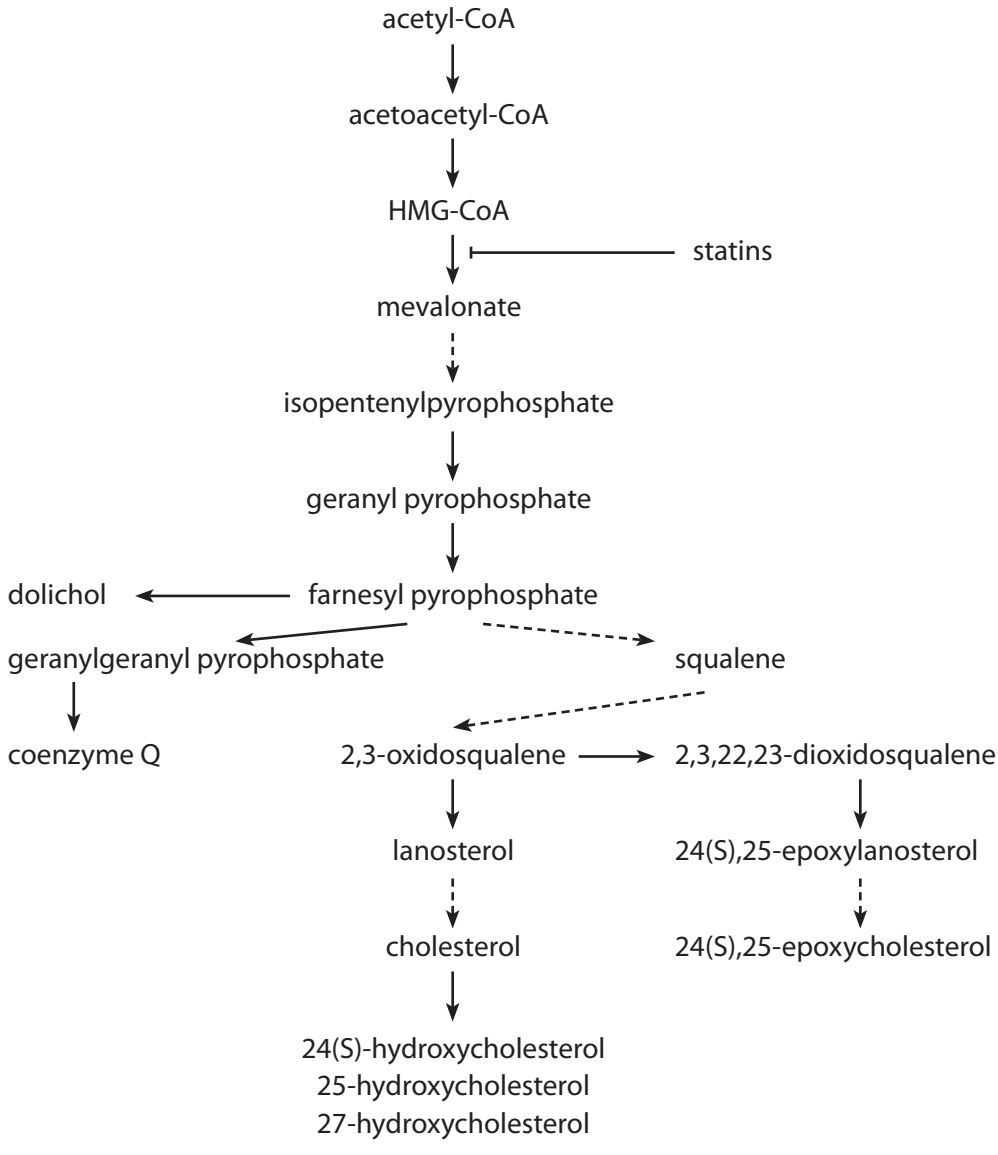

Figure 1. Mevalonate cascade and mechanism of action of statins. Broken arrows abbreviate multiple step reactions. HMG-CoA – 3-hydroxy 3-methylglutarylcoenzyme A.

ovascular events and reduce mortality in primary and secondary prevention of ischemic heart disease (1,2). Initially introduced as cholesterol-lowering drugs, statins posses multiple other lipid-independent or "pleiotropic" atheroprotective activities such as improvement of endothelial function, inhibition of inflammatory reaction, platelet aggregation and thrombosis, and amelioration of oxidative stress. Therefore, beneficial effects of statins are observed not only in patients with hyperlipidemia but also in those with normal cholesterol level. In addition to ischemic heart disease, statins may reduce the risk of ischemic stroke, left ventricular hypertrophy, arrhythmias, Alzheimer's disease, type 2 diabetes mellitus, slow the progression of chronic nephropathies, rheumatoid arthritis and multiple sclerosis, and increase bone mineral density (3-7).

Statins inhibit the rate-limiting step of the mevalonate cascade (Fig. 1); the relevant products of which being not only cholesterol but also many other compounds referred to as nonsteroid isoprenoids. Among them, coenzyme Q (ubiquinone) is an electron carrier in mitochondrial respiratory chain and an important endogenous lipid-soluble antioxidant present in plasma membranes and plasma lipoproteins. Farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP) are posttranslationally attached to various small GTP-binding proteins such as Ras, Rho and Rab which regulate cell growth,

proliferation and survival, intracellular vesicular transport, etc. Dolichol is an essential carrier of carbohydrate moieties used for protein N-glycosylation – the process crucial for transport of membrane-targeted proteins and their biological activities. Depletion of these nonsteroid isoprenoids is responsible for cholesterol-independent pleiotropic activities of statins but also contributes to their adverse effects. Although statins are usually safe and well-tolerated, important complications such as myopathy, hepatotoxicity, polyneuropathy, and gastrointestinal disturbances develop in a small subset of patients.

Lowering plasma cholesterol results mainly from the inhibition of hepatic HMG-CoA reductase, whereas cholesterol-independent effects may be exerted in every cell type. Most currently used statins except pravastatin and rosuvastatin are lipophilic, easily permeate plasma membranes, and affect both hepatic and extrahepatic HMG-CoA reductase. Pravastatin and rosuvastatin are hydrophilic and easily penetrate only into hepatocytes through plasma membrane organic anion transporter. Thus, although they may be as effective as other statins in reducing plasma cholesterol, they much less effectively inhibit mevalonate cascade in extrahepatic cells.

Simvastatin and lovastatin are used as inactive lactones which are *in vivo* enzymatically hydrolyzed to active free acids (8). Simvastatin, lovastatin and atorvastatin are metabolized by cytochrome P450 CY3A4 isoform and their metabolism may be impaired by other substrates or inhibitors of this enzyme (9). Fluvastatin is not metabolized by CYP3A4 but by CYP2C9. Pravastatin and rosuvastatin are the only statins which are in substantial amounts excreted in urine in the unchanged form, although about 10% of administered rosuvastatin is also metabolized by CYP2C9 (10). These hydrophilic statins are metabolized to a much lower degree than other HMG-CoA reductase inhibitors and thus are less prone to interact with other CYP substrates.

Statins are currently used by 25-30 millions people worldwide, mostly by those with recognized cardiovascular diseases or with increased risk of these pathologies. On the other hand, overweight and obesity are important risk factors of hyperlipidemia, atherosclerosis, arterial hypertension and heart failure. In addition, impaired glucose tolerance or type 2 diabetes are frequently observed in overweight/obese subjects and are often accompanied by dyslipidemia. Thus, the large fraction of statin-treated patients have excess of adipose tissue and therefore, the effect of statins on this tissue is clinically significant. However, in comparison to a great body of data about statins accumulated over the last two decades, relatively little is known about their effects on adipose tissue. In this article I review the current knowledge in this field.

Effect of statins on body weight and energy balance

Most studies have shown no effect of statins administered at pharmacological doses on food intake, energy expenditure, body weight and adiposity in animals fed standard diet (11,12). In addition, no gross effect of statins on body weight or adiposity was observed in statin-treated patients. Recently, Araki *et al* (13) have demonstrated that pravastatin (100 mg/kg for 28 days) decreased weight gain and visceral fat accumulation in mice fed high-calorie diet. Moreover, pravastatin increased oxygen consumption and reduced respiratory quotient. These results suggest that statins may prevent the development of obesity by increasing energy expenditure. However, the dose of pravastatin used in this study was higher than in most experimental studies. In addition, these results need to be confirmed for other statins and other models of obesity.

Effect of statins on adipocyte differentiation and survival

Differentiation of preadipocytes to adipocytes is essential for adipose tissue growth and also is a crucial process in the development of obesity. When the amount of triglycerides accumulated per each existing adipocyte reaches the threshold level, novel preadipocytes are recruited to differentiate into mature fat cells and accumulate the surplus of available energy. From this moment, obesity becomes "hyperplastic" (more fat cells) instead of hypertrophic (more triglycerides/cell but unchanged cell number). Hyperplastic obesity is more resistance to treatment since increase in the amount of adipocytes is irreversible. Preadipocyte differentiation is initiated by two transcription factors: peroxisome proliferator-activated receptor-γ (PPAR-γ) and CCAT enhancer-binding protein-α (C/EBP-α), which regulate the expression of adipocyte-specific genes such as enzymes involved in triglyceride storage, leptin, adiponectin etc. On the other hand, preadipocyte factor-1 (Pref-1) is a major inhibitor of preadipocyte differentiation.

Several studies have demonstrated that various statins inhibit preadipocyte differentiation *in vitro*. Nishio *et al* (14) first demonstrated that lovastatin and simvastatin inhibited differentiation of cultured murine 3T3-L1 preadipocytes as evidenced by reduced number of lipid droplets and the amount of triglycerides in statin-treated cells. This effect was ameliorated by mevalonate, farnesyl- or geranylgeranylpyrophosphate but not by squalene or cholesterol. These results indicate that the effect of statins is mediated by depletion of non-steroid isoprenoids. These observations were later confirmed by other authors (15) and also in other cell lines including bone marrow stromal cells (16-18).

Red yeast rice has been used as a natural food colorant and preservative, and as a traditional medicine for improving food digestion and blood circulation in oriental countries. Interestingly, red yeast rice extract, which contains lovastatin, dose-dependently decreased differentiation of 3T3-L1 cells as evidenced by reduced activity of a key enzyme of triglyceride synthesis, glycerol 3-phosphate dehydrogenase (GPDH), decreased triglyceride content, and 30-50% fall in the expression of PPAR-γ, C/EBP-α, adipocyte fatty acid-binding protein-2 (aP2) and leptin (19).

Nicholson *et al* (20) observed that pitavastatin reduced PPAR-γ and increased Pref-1 expression in 3T3-L1 cells while having no effect on PPAR-γ DNA-binding activity. Surprisingly, pitavastatin increased C/EBP-α expression. However, reduction of PPAR-γ and stimulation of Pref-1 were sufficient to inhibit cell differentiation, as evidenced by reduced number of lipid droplets, triglyceride content, fatty acid binding proteins (CD36 and aP2), solute carrier 2A4 (SLC2A4)/glucose transporter GLUT4 expression and adipsin secretion. Interestingly, although these effects of pitavastatin were reproduced by rosuvastatin and simvastatin, they were not prevented by mevalonate or cholesterol, suggesting that anti-adipogenic effect of statins is independent of the inhibition of HMG-CoA reductase. In immortalized murine epididymal preadipocytes, atorvastatin reduced lipid accumulation, C/EBP-α expression and impaired insulin-stimulated lipogenesis (21).

In contrast, Fajas *et al* (22) have shown that treatment of 3T3-L1 cells with either simvastatin or mevastatin increased PPAR-γ expression. This effect was mediated by statin-induced activation of sterol response element-binding protein-1 (SREBP-1) – transcription factor activated by cholesterol depletion. The difference between results of this study and studies mentioned above is most likely associated with culture conditions – authors used cholesterol-free medium which favored statin-induced cholesterol depletion. In cholesterol-replete media statins are unlikely to reduce intracellular cholesterol substantially but reduce non-steroid isoprenoids. In addition, lower statin concentration (0.5 μM vs. 1-10 μM in other studies) was used (22).

Recently, Madsen *et al* (23) have demonstrated that lipophilic simvastatin induces apoptosis of differentiating 3T3-L1 preadipocytes but not of differentiated cells. The effect of simvastatin was prevented by synthetic liver X receptor (LXR) agonists, T0901317 and GW3965. LXR are ligand-activated transcription factors which heterodimerize with the retinoid X receptor and, upon ligand binding, regulate the expression of target genes. LXR are activated by endogenous enzymatically-formed oxygenated cholesterol derivatives (oxysterols) such as 24(S)-, 25- or 27-hydroxycholesterol as well as by 24(S),25-epoxycholesterol, the product of the "shunt pathway" of the mevalonate cascade (Fig. 1). Activated LXR stimulate the expression of genes involved in reverse cholesterol transport, its conversion to bile acids and biliary excretion. In addition, LXR inhibit intestinal cholesterol absorption and cholesterol synthesis. In addition, LXR regulate other processes such as immunity, inflammation, nervous and reproductive system functions. Several studies have demonstrated that statins decrease oxysterol concentrations; especially the level of 24(S),25-epoxycholesterol, and decrease the expression of LXR target genes (24, 25). Madsen *et al*. have demonstrated that proapoptotic effect of simvastatin was not associated with the reduction of either PPAR-γ or SREBP expression or with the inhibition of insulin-like growth factor-1 (IGF-1)-induced activation of prosurvival protein kinase B (PKB)/Akt. In contrast, statin-induced cell death was aggravated by LXRα and LXRβ gene knockouts and was abolished by forced expression of constitutively active LXRα (23). Mauser *et al* (21) have demonstrated that atorvastatin induces apoptosis of differentiating murine epididymal preadipocytes but not of mature adipocytes. This effect resulted from the inhibition of PKB/Akt phosphorylation.

Role of adipose tissue in the effect of statins on plasma lipoproteins

It has been recognized for a long time that plasma cholesterol concentration is proportional to body weight, which suggests the link between adipose tissue and cholesterol metabolism. Indeed, adipose tissue contains more cholesterol than liver, muscle or kidney when expressed on a *per* mg protein basis, and more than all other organs when expressed on a per g of tissue basis. Adipose tissue cholesterol pool constitutes about 25% of the whole-body cholesterol content and may increase up to 50% in obese subjects. However, cholesterol turnover in adipose tissue is relatively slow. The activity of cholesterol biosynthesis pathway in adipocytes is lower than in other tissues and most of cholesterol is provided by plasma lipoproteins. Thus, although lipophilic statins are expected to accumulate in fat cells in substantial amounts, it is unlikely that adipose tissue contributes significantly to statin-induced inhibition of cholesterol synthesis (26). Due to low cholesterol synthesis but high cholesterol demand, especially for a build-up of plasma membrane in rapidly growing adipocyte during triglyceride accumulation, fat cells take-up cholesterol not only from LDL but also from HDL through at least two mechanisms (27): (*i*) scavenger receptor type B1 (SR-B1)-dependent (2/3 of cholesterol uptake), and (*ii*) SR-B1 independent, which requires cholesterol ester transfer protein (CETP), apolipoprotein E and LDL receptor-related protein (LRP). Zhao *et al* (28) have demonstrated that high-cho-

lesterol diet decreases SR-B1 expression in rabbit subcutaneous adipose tissue, whereas atorvastatin administered at 2.5 mg/kg/day for 6 weeks reverses this effect. However, the implications of this effect of atorvastatin for cholesterol balance of adipocytes is unclear.

It is well known that statins reduce not only plasma cholesterol but also triglyceride concentration. The mechanism of the latter effect includes inhibition of hepatic VLDL formation but also enhancement of their clearance. Apart from skeletal muscles, adipose tissue is the most important site of lipoprotein lipase (LPL)-driven VLDL metabolism. The effect of statins on LPL in adipose tissue is controversial. In vitro, pravastatin, simvastatin, atorvastatin and pitavastatin increased LPL expression and activity in 3T3-L1 adipocytes (29,30). In contrast, in vivo studies are not so unambiguous. For instance, atorvastatin and pravastatin increased LPL activity in patients with type 2 diabetes and hypercholesterolemia (31, 32) and simvastatin (but not atorvastatin) had a similar effect in cholesterol-fed rabbits (33). Simvastatin administered at a very high dose (120 mg/kg) for 4 days increased LPL activity in adipose tissue of normal rats. In addition, simvastatin reduced apolipoprotein C-III (the LPL inhibitor) level (34). In contrast, lovastatin (4 mg/kg/day) injected subcutaneously for 13 days had no effect on LPL expression in leptin receptor deficient Zucker fa/fa rats (35). Similarly, atorvastatin given orally for 2 weeks at either 5 or 30 mg/kg/day did not change $mRNA^{LPL}$ level in adipose tissue of fructose-fed rats, a model of hypertriglyceridemia (36). It should be noted that statins reduced plasma triglycerides in both these studies, which indicates that stimulation of adipose tissue LPL is not indispensable for triglyceride-lowering effect of these drugs.

Some studies suggest that statins might affect the balance between triglyceride synthesis and lipolysis in adipose tissue. For example, atorvastatin reduced the expression of acylation-stimulating protein (ASP) and enhanced the expression of hormone-sensitive lipase (HSL) in adipose tissue of fructose-fed rats (36).

Role of adipose tissue in effect of statins on glucose utilization and insulin sensitivity

The effect of statins on glucose metabolism and insulin sensitivity is controversial. Hydrophilic pravastatin has been demonstrated to reduce the incidence of new-onset diabetes by 30% (37). However, several trials have demonstrated worsening of glucose metabolism by simvastatin, atorvastatin and rosuvastatin in patients with pre-existing diabetes (38,39), as well as increase in the rate of onset of new diabetes in non-diabetic patients treated with these drugs (40-44). Takano *et al* (45, 46) have demonstrated that atorvastatin, but not pravastatin or pitavastatin, increases plasma glucose and glycated hemoglobin Hb_{A1c} concentrations in patients with type 2 diabetes. Atorvastatin worsened glucose metabolism in rats with streptozotocin-induced diabetes (47) and in obese, insulin resistant and moderately hyperglycemic NSY mice (39).

Adipose tissue is one of the major sites of glucose disposal and a key target for insulin. Thus, adipose tissue may be the main target for unfavorable effect of statins on glucose metabolism. There are at least three mechanisms through which statins might impair insulin sensitivity of adipocytes. First, as described above, statins inhibit adipocyte differentiation. Differentiated adipocytes are much more insulin-sensitive than non-mature fat cells. Thiazolidinedione derivatives (PPAR-γ agonists), used in the treatment of type 2 diabetes, improve insulin sensitivity partially by stimulating adipocyte differentiation. Nakata *et al* (39) have demonstrated that atorvastatin reduces the expression of SLC2A4/GLUT4, glucose transporter involved in insulin-stimulated glucose uptake, in 3T3-L1 adipocytes, which results from impaired cell differentiation as evidenced by the simultaneous reduction of PPAR-γ and C/EBP-α expression. Simvastatin was 1000 times less potent and pravastatin had no effect at all. Although simvastatin is lipophilic, it is used as an inactive pro-drug (simvastatin lactone) which must be enzymatically hydrolyzed to free acid *in vivo*; this could explain its low potency in cultured adipocytes. In addition, atorvastatin markedly reduced the expression of insulin receptor β-subunit (IR-β). These effects were accompanied by reduced insulin-induced PKB/Akt phosphorylation and glucose uptake. Interestingly, atorvastatin had no effect on SLC2A4/GLUT4 expression in cultured skeletal myocytes indicating that its effect is specific for adipocytes (39). In fully differentiated 3T3-L1 adipocytes the effect of atorvastatin on SLC2A4 expression and insulin-stimulated glucose uptake was still observed but was much less pronounced than in differentiating cells. However, in contrast to immature adipocytes, atorvastatin increased the expression of IR-β and insulin receptor substrate-1 (IRS-1) in fully differentiated adipocytes (39).

Second, insulin stimulates protein farnesyl- and geranylgeranyltransferases (48, 49), and isoprenylated proteins are involved in some aspects of insulin signaling. For example, Rab4 protein is involved in intracellular vesicular transport of SLC2A4/GLUT4 from inactive intracellular pool to the plasma membrane; the key process in insulin-induced glucose uptake. Takaguri *et al* (50) have recently demonstrated that atorvastatin but not pravastatin decreases insulin-induced 2-deoxyglucose uptake by mature 3T3-L1 adipocytes by attenuating insulin-induced translocation of SLC2A4/GLUT4 to the plasma membrane. Atorvastatin had no effect on insulin-induced tyrosine phosphorylation of the IR-β as well as on absolute level of SLC2A4/GLUT4 mRNA and protein, suggesting that impaired translocation of glucose

transporter plays a major role in impairing insulin sensitivity. The effect of atorvastatin was accompanied by the increase in the amount of Rab4 in the cytosolic fraction and decrease in its content in the membrane fraction. Since translocation of Rab4 to the membrane fraction is dependent on its isoprenylation, these data suggest that atorvastatin impairs SLC2A4/GLUT4 translocation secondarily to attenuating isoprenylation of Rab4.

Finally, various statins impaired glycosylation of insulin receptor in 3T3-L1 adipocytes, which resulted in impaired translocation of this receptor to the plasma membrane and accumulation of unglycosylated receptors in endoplasmic reticulum (51). This effect, as well as impairment of insulin-induced glucose uptake, was reproduced by selective inhibitors of protein glycosylation but not by farnesyltransferase inhibitors. Thus, statin-induced dolichol deficiency may impair insulin signaling by interfering with insulin receptor glycosylation.

Statins and adipose tissue inflammation

Recent studies indicate that obesity and the metabolic syndrome are associated with chronic low-grade inflammation of the adipose tissue accompanied by accumulation of macrophages and mast cells which express proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1) or interleukin-6 (IL-6); some of them being synthesized also by adipocytes themselves. Adipose tissue inflammation contributes to insulin resistance and abnormalities of glucose metabolism associated with obesity. Adipose tissue inflammation is driven, at least in part, by activation of lipopolysaccharide (LPS) receptor, Toll-like receptor-4 (TLR-4), by saturated fatty acids, and by hypoxia (see Trayhurn *et al* in this volume of *Adipobiology*). Abe *et al* (52) have demonstrated that pravastatin or pitavastatin administered to leptin-deficient *ob/ob* mice reduced the expression of MCP-1, TNF-α and IL-6 genes in epididymal and subcutaneous adipose tissue. Statins had no effect on body weight as well as on the amount of macrophages in adipose tissue. *In vitro* studies revealed that conditioned medium of cultured LPS-treated macrophages stimulated inflammatory response of adipocytes but this effect was suppressed if macrophages (but not adipocytes) wee pretreated with statins. Indeed, pravastatin and pitavastatin reduced the expression of MCP-1, TNF-α, IL-6 and inducible nitric oxide synthase (iNOS) in LPS-treated macrophages. The TLR-4 receptor triggers two signaling pathways: (*i*) recruitment of Toll/IL-1 receptor (TIR)-domain-containing adaptor protein MyD88, which then activates nuclear factor-κB (NF-κB) and c-Jun N-terminal kinase (JNK), and (*ii*) recruitment of TIR domain-containing adaptor inducing IFN-γ (TRIF), leading to the activation of transcription factor IRF3 which then activates IFN-γ promoter and stimulates its synthesis. Statins inhibited phosphorylation of IRF3, synthesis of IFN-γ, and phosphorylation of its signaling target, STAT1 protein. In contrast, pravastatin or pitavastatin had no effect on MyD88-dependent signaling. Collectively, these data indicate that statins inhibit MyD88-independent TLR-4 signaling in adipose tissue macrophages leading to the attenuation of IFN-γ formation and reduction of proinflammatory response of adipocytes as well as macrophages themselves (52). Treatment with atorvastatin reduced production of C-reactive protein (CRP) (53), IL-6 (54), and TNF-α (55) by adipocytes of cholesterol-fed rabbits. *In vitro*, atorvastatin (54) and cerivastatin (56) decreased IL-6 expression by cultured rabbit and human adipocytes. Finally, simvastatin and pravastatin decreased cytokine-stimulated expression of iNOS in 3T3-L1 adipocytes (57). Reduction of adipose tissue inflammation may contribute to beneficial effects of statins on insulin sensitivity and also to the inhibition of atherogenesis.

Statins and adipokines

Adipokines play an important role in adipose tissue physiology and in obesity-associated complications (58). Herein, I focus on effect of statins on most extensively studied adipokines: leptin, adiponectin, resistin and visfatin.

Leptin

Zhao *et al* (59) have demonstrated that high-cholesterol diet increases plasma leptin concentration in the rabbit more than 2-fold without changing body weight or adiposity. Concomitant treatment with atorvastatin reduced serum leptin and leptin mRNA in subcutaneous adipose tissue simultaneously with decreasing LDL-cholesterol but had no effect on body weight. These data suggest that statins may decrease leptin level. The mechanism of this effect is unclear but may include reduction of either adipose tissue inflammation or oxidative stress because both these conditions stimulate leptin production.

Effect of statins on plasma leptin concentration in humans was addressed in 9 clinical studies (Table 1). In most of them, statins did not change leptin level significantly. One study demonstrated decrease and one increase in leptin. Koh *et al* (63) compared the effect of simvastatin and pravastatin in a crossover study in the same group of hypercholesterolemic patients. They observed that lipophilic simvastatin but not hydrophilic pravastatin increased serum leptin concentration. Although these data suggest that various statins may have divergent effects on leptin level, the overall analysis of data presented in Table 1 indicates that modulation of leptin plays only a minor role in the effect of statins.

Table 1. Effect of statins on plasma leptin concentration in clinical studies

Patients	Number of patients	Treatment	Leptin concentration*	Comments	Ref.
Type 2 diabetes	32	Atorvastatin 40 mg/day 8 weeks	-40%	Placebo-controlled study	60
Non-alcoholic steatohepatitis with hyperlipidemia	31	Atorvastatin 10 mg/day 24 months	No change	No placebo group	61
Overweight with impaired glucose tolerance but not diabetes	30	Simvastatin 20 mg/day 16 weeks	No change	No placebo group	62
Hypercholesterolemia	43	Simvastatin 20 mg/day 8 weeks	+35%	Placebo-controlled study Decrease in insulin sensitivity following simvastatin treatment	63
Hypercholesterolemia	43	Pravastatin 40 mg/day 8 weeks	No change	Placebo-controlled study Increase in insulin sensitivity following pravastatin treatment	63
Healthy non-diabetic volunteers without ischemic heart disease	40	Pravastatin 40 mg/d 12 weeks	No change	Placebo-controlled study	64
Hypercholesterolemia without ischemic heart disease	36	Atorvastatin 10 mg/day 16 weeks	No change	No placebo group, compared to pravastatin-treated group	65
Hypercholesterolemia without ischemic heart disease	36	Pravastatin 10 mg/day 16 weeks	No change	No placebo group, compared to atorvastatin-treated group	65
Type 2 diabetes with hyperlipidemia	29	Atorvastatin 10-40 mg/day 12 weeks	No change	No placebo group	66
Healthy men	24	Simvastatin 10 mg/day 2 weeks	No change	No placebo group, compared to group receiving ezetimibe	67
Hypercholesterolemia	42	Pitavastatin 2 mg/day 12 weeks	No change	No placebo group	68

* Post-treatment vs. pre-treatment percent change of mean or median concentration

Adiponectin

Mauser *et al* (21) have demonstrated that atorvastatin reduced adiponectin expression in differentiated 3T3-L1 adipocytes. In contrast, pravastatin increased adiponectin secretion in the same cell culture, and upregulated adiponectin gene expression and elevated its plasma level in leptin receptor deficient *db/db* mice as well as in high-fat and high-sucrose fed C57BL/6J mice (69). This effect of pravastatin correlated with the improvement of insulin sensitivity and was not accompanied by any changes in body weight. Simvastatin did not change either adiponectin level or insulin sensitivity. Authors suggest that effect on adiponectin may explain differential influence of hydrophilic and lipophilic statins on glucose metabolism (69).

Although leptin is the best characterized adipokine, much more studies addressed the effect of statins on adiponectin in various patient groups. Among them, increase, decrease or no change in adiponectin following statin treatment was noted in 20, 4 and 20 studies, respectively (Table 2). If changes in adiponectin were observed, they were relatively small, rarely exceeding 20-30%. The largest effect was observed for rosuvastatin (73). Authors who observed increase in adiponectin usually suggest that it might contribute to antiatherogenic and antidiabetic

Table 2. Effect of statins on plasma adiponectin concentration in clinical studies

Patients	Number of patients	Treatment	Adiponectin concentration*	Comments	Ref.
Non-alcoholic steatohepatitis with hyperlipidemia	31	Atorvastatin 10 mg/day 24 months	+25%	No placebo group	61
Hypercholesterolemia	43	Pravastatin 40 mg/day 8 weeks	+9%	Placebo-controlled study, Increase in insulin sensitivity during pravastatin treatment	63
Ischemic heart disease with impaired glucose tolerance	20	Pravastatin 20 mg/day 6 months	+35%	Placebo-controlled study Increase in insulin sensitivity during treatment was correlated with increase in adiponectin	70
Type 2 diabetes with hyperlipidemia	64	Pitavastatin 2 mg/day 6 months	+25%	No placebo group	71
Hyperlipidemia with mild hypertension	27	Pravastatin 20 mg/day 6 months	+10%	No placebo group Compared to previous treatment with simvastatin (10 mg/day)	72
Primary hypercholesterolemia	35	Rosuvastatin 10 mg/day 12 weeks	+68%	No placebo group	73
Primary hypercholesterolemia	34	Atorvastatin 10 mg/day 12 weeks	+15%	No placebo group	73
Ischemic heart disease	22	Atorvastatin 10 mg/day 12 weeks	+39%	No placebo group	74
Ischemic heart disease or diabetes or peripheral artery occlusive disease or cerebrovascular disease or a 10-year risk of ischemic heart disease ›20%	102	Atorvastatin 10-80 mg/day 12 weeks	Dose-dependent increase; significant at 40 and 80 mg/day (+25%). Less marked increase in patients with diabetes or metabolic syndrome	No placebo group	75
Hyperlipidemia	72	Pitavastatin 2 mg/day 6 months	+24%	Placebo-controlled study	76
Hypercholesterolemia without ischemic heart disease	36	Atorvastatin 10 mg/day 16 weeks	+7%	No placebo group, compared to pravastatin-treated group	65
Type 2 diabetes	52	Atorvastatin 40 mg/day 8 weeks	Total: no change HMW: +42% MMW: –21% LMW: –23% HMW/total: +25%	Placebo-controlled study	77
Familial combined hyperlipidemia, non-obese patients	22	Atorvastatin 10 mg/day 24 weeks	+13%	No placebo group Compared to fenofibrate-treated group	78
Stable ischemic heart disease with mixed hyperlipidemia	16	Atorvastatin 10 mg/day 4 weeks or 6 months	+25%	Placebo-controlled study	79
Type 2 diabetes	30	Atorvastatin 10 mg/day 12 weeks	+32% (vs. treatment with rosiglitazone alone)	No placebo group Compared to treatment with rosiglitazone alone	80

Patients	Number of patients	Treatment	Adiponectin concentration*	Comments	Ref.
Ischemic heart disease with hypercholesterolemia	115	Pravastatin 10 or 20 mg/day 6 months	+16%	No placebo group	81
Ischemic heart disease; patients undergoing coronary artery bypass grafting (CABG) with LDL-cholesterol >100 mg/dl	32	Pravastatin 10 mg/day 2 months before CABG	+42.3% in serum +59% in visceral adipose tissue Unchanged in subcutaneous adipose tissue +200% (mRNA in visceral adipose tissue)	No follow-up observation, Percent change compared to group receiving no statin (with LDL-cholesterol < 100 mg/dl)	82
Stable ischemic heart disease	16	Pitavastatin 2 mg/day 6 months	+20%	No placebo group	83
Hyperlipidemia with or without diabetes	117	Pitavastatin 2 mg/day 6 months	+25% in diabetic patients No change in non-diabetics	No placebo group	84
Hyperlipidemia with or without type 2 diabetes	75	Pitavastatin 2 mg/day 3 or 6 months	Diabetic patients: +37% (3 months) +64% (6 months) Non-diabetic patients: no change	No placebo group Similar reduction of plasma lipids in diabetic and non-diabetic patients	85
Hypercholesterolemia	43	Simvastatin 20 mg/day 8 weeks	-10%	Placebo-controlled study Decrease in insulin sensitivity by 7% during statin treatment	63
Nondiabetic patients with ischemic heart disease, carotid artery atherosclerosis or leg artery atherosclerosis	43	Simvastatin 40 mg/day 12 weeks	-12%	No placebo group Compared with group treated with pioglitazone	86
Ischemic heart disease - stable angina and normal lipid profile, patients scheduled for coronary angioplasty, treatment started after angioplasty	30	Atorvastatin 10 mg/day 6 months	-20%	Placebo-controlled study	87
Hypercholesterolemia	124	Simvastatin 10-80 mg/day 8 weeks	Dose-dependent decrease (-4 to -10%)	Placebo-controlled study	88
Combined hyperlipidemia	56	Atorvastatin 10 mg/day 8 weeks	No change	Placebo-controlled study	89
Type 1 or type 2 diabetes	77	Atorvastatin 20 mg/day 12 weeks	No change	Placebo-controlled study	90
Overweight with impaired glucose tolerance but not diabetes	30	Simvastatin 20 mg/day 16 weeks	No change	No placebo group	62
Hypertension with hypercholesterolemia	47	Simvastatin 20 mg/day 8 weeks	Non-significant reduction	Placebo-controlled study	91
Type 2 diabetes	53	Simvastatin 20 mg/day 8 weeks	Non-significant reduction	Placebo-controlled study	92

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Patients	Number of patients	Treatment	Adiponectin concentration*	Comments	Ref.
Healthy non-diabetic volunteers without ischemic heart disease	40	Pravastatin 40 mg/day 12 weeks	No change	Placebo-controlled study	64
Non diabetic patients with increased cardiovascular risk (thickened carotid artery intima-media thickness, history of myocardial infarction, proved ischemic heart disease in coronary angiography, unstable angina, cervical or leg artery atherosclerosis, ischemic changes in ECG, stroke, transient ischemic attack, peripheral arterial occlusion)	80	Atorvastatin 40 mg/day 6 months	No change	No placebo group	93
Overweight patients with type 2 diabetes and mixed hyperlipidemia	13	Atorvastatin 10 mg/day 6 weeks	No change	No placebo group	94
Type 2 diabetes with hypertriglyceridemia	194	Atorvastatin 10 or 80 mg/day 6 months	No change	Placebo-controlled study	95
Hyperlipidemia	63	Simvastatin 10 mg/day 6 months	No change	Placebo-controlled study	76
Hypercholesterolemia without ischemic heart disease	36	Pravastatin 10 mg/day 16 weeks	No change	No placebo group	65
Type 2 diabetes with hyperlipidemia	29	Atorvastatin 10-40 mg/day 12 weeks	No change	No placebo group	66
Hypercholesterolemia	32	Atorvastatin 10 mg/day 12 weeks	No change	No placebo group	96
Type 2 diabetes with dyslipidemia	12	Atorvastatin 10 mg/day 8 weeks	No change	No placebo group	97
Kidney transplant recipients	68	Atorvastatin 10 mg/day 12 weeks	No change	No placebo group	98
Hypercholesterolemia	24	Fluvastatin 80 mg/day 12 weeks	No change	No placebo group	99
Non-smoking males with obesity/ metabolic syndrome	15	Simvastatin 80 mg/day 6 weeks	No change following either therapy	No placebo group, cross-over study with simvastatin alone or simvastatin 10 mg/ day+ezetimibe 10 mg/day	100
Healthy men	24	Simvastatin 10 mg/day 2 weeks	No change of total and HMW form	No placebo group, compared to ezetimibe alone or ezetimibe/simvastatin combination	67
Metabolic syndrome	25	Simvastatin 40 mg/day 8 weeks	No change	Placebo-controlled study	101
Hypercholesterolemia	42	Pitavastatin 2 mg/day 12 weeks	No change	No placebo group	68

* Post-treatment vs. pre-treatment percent change of mean or median concentration (if not otherwise stated)
HMW – high-molecular weight adiponectin, MMW – medium-molecular weight adiponectin, LMW – low-molecular weight adiponectin

effect of statins. However, this increase is relatively small e.g. in comparison to PPAR-γ agonists (2-3 fold increase), for which the involvement of adiponectin in insulin-sensitizing effect was demonstrated. In three studies the effect of various statins was directly compared. Koh *et al* (63) observed that pravastatin increased while simvastatin reduced serum adiponectin, which was accompanied by parallel changes in insulin sensitivity. Qu *et al* (73) found that rosuvastatin was much more effective in elevating adiponectin in comparison to atorvastatin, although both drugs similarly reduced LDL-cholesterol. Nomura *et al* (76) found that pitavastatin but not simvastatin slightly elevated adiponectin level, and Ando *et al* (65) observed that atorvastatin but not pravastatin increased adiponectin by 7%. Importantly, only total adiponectin was measured by most authors. Von Eynatten *et al* (77) found that atorvastatin had no effect on total adiponectin but significantly increased high molecular weight (HMW) adiponectin and decreased medium- and low-molecular weight forms. Because HMW adiponectin is a major "beneficial" form of this adipokine, increase in HMW/total adiponectin ratio may markedly improve risk profile of the treated patients. In addition, reciprocal effects on various adiponectin isoforms may explain, at least partially, controversial results of studies in which only total adiponectin was measured. Inami *et al* (84) have found that pitavastatin increases adiponectin level only in diabetic but not in nondiabetic patients with hyperlipidemia. Clearly, baseline profile of risk factors as well as presence or absence of atherosclerosis may affect the effect of statins on adiponectin. Unfortunately, more homogenous patient groups were examined in most studies and the effect in subjects with various risk profiles was not directly compared.

Resistin

Simvastatin inhibited C-reactive protein-induced upregulation of resistin gene expression in human peripheral blood monocytes (102). The effect of simvastatin was reversed by mevalonate and geranylgeranylpyrophosphate but not by farnesylpyrophosphate. Similarly, atorvastatin reduced resistin gene expression in murine 3T3-L1 adipocytes, cultured human preadipocytes and monocyte-macrophages (103, 104).

In most clinical studies, no effect of statins on plasma resistin level was reported (Table 3). Thus, it seems unlikely that reduction of resistin is involved in beneficial effects of statins.

Table 3. Effect of statins on plasma resistin concentration in clinical studies

Patients	Number of patients	Treatment	Resistin concentration*	Comments	Ref.
Type 2 diabetes	32	Atorvastatin 40 mg/day 8 weeks	-40%	Placebo-controlled study	60
Type 1 or type 2 diabetes	77	Atorvastatin 20 mg/day 12 weeks	No change	Placebo-controlled study	90
Overweight patients with type 2 diabetes and mixed hyperlipidemia	13	Atorvastatin 10 mg/day 6 weeks	No change	No placebo group	94
Hypercholesterolemia without ischemic heart disease	36	Atorvastatin 10 mg/day 16 weeks	No change	No placebo group	65
Hypercholesterolemia without ischemic heart disease	36	Pravastatin 10 mg/day 16 weeks	No change	No placebo group	65
Healthy men	24	Simvastatin 10 mg/day 2 weeks	No change	No placebo group, compared to ezetimibe alone or ezetimibe/ simvastatin combination	67
Hypercholesterolemia	32	Atorvastatin 10 mg/day 12 weeks	No change	No placebo group	96
Type 2 diabetes	12	Atorvastatin 10 mg/day 6 months	No change	No placebo group	103
Hypercholesterolemia	42	Pitavastatin 2 mg/day 12 weeks	-11%	No placebo group	68

* Post-treatment vs. pre-treatment percent change of mean or median concentration

Visfatin

Although initially identified as an insulin-sensitizing agent, visfatin is an ambiguous adipokine since it may also induce endothelial dysfunction and promote inflammation thus aggravating atherogenesis. Atorvastatin reduces visfatin gene expression in murine differentiated white adipocytes (21). Until now, the effect of statin therapy on serum visfatin level was examined only in 3 clinical studies. Kostapanos *et al* (105) have demonstrated that rosuvastatin administered at 10 mg/day for 12 weeks reduces serum visfatin by about 10% in patients with primary hyperlipidemia without cardiovascular diseases. In contrast, simvastatin had no effect on visfatin concentration in non-diabetic patients with the metabolic syndrome (106). Similarly, 12-week treatment with atorvastatin did not modify visfatin level in patients with primary hyperlipidemia (107).

Conclusions

Statins have multiple effects in virtually all tissues and adipose tissue is not an exception. Most of currently used statins are lipophilic and thus expected to accumulate in substantial amounts in adipose tissue. Currently available data indicate that although statins have no gross effect on body adiposity, adipose tissue may be the target for both beneficial and adverse effects of these drugs. Statins inhibit adipocyte differentiation, impair insulin signaling in fat cells, inhibit adipose tissue inflammation, and modulate adipokine synthesis and secretion. However, many effects of statins on adipose tissue are controversial, especially their influence on VLDL clearance and adipokine production. Many results were obtained in cultured adipocyte cell lines and thus do not necessarily reflect in vivo situation. More experimental studies are needed to elucidate in more detail effect of statins on adipokines production and the mechanism of these effect, since the results of clinical studies are highly controversial. Due to increasing usage of statins worldwide, elucidating their effects on adipose tissue is important to improve the results of treatment with these drugs.

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