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Functional Implications of HMG-CoA Reductase Inhibition on Glucose Metabolism

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ABSTRACT

HMG-CoA reductase inhibitors, i.e. statins, are effective in reducing cardiovascular disease events but also in cardiac-related and overall mortality. Statins are in general well-tolerated, but currently the concerns are raised if statins may increase the risk of new-onset diabetes mellitus (NOD). In this review, the possible effects of statins on organs/tissues being involved in glucose metabolism, i.e. liver, pancreas, adipose tissue, and muscles, had been discussed. The net outcome seems to be inconsistent and often contradictory, which may be largely affected by in vitro experimental settings or/and in vivo animal conditions. The majority of studies point out statin-induced changes of regulations of isoprenoid metabolites and cell-associated cholesterol contents as predisposing factors related to the statin-induced NOD. On the other hand, it should be considered that dysfunctions of isoprenoid pathway and mitochondrial ATP production and the cholesterol homeostasis are already developed under (pre)diabetic and hypercholesterolemic conditions. In order to connect the basic findings with the clinical manifestation more clearly, further research efforts are needed.

Keywords: HMG-CoA reductase; Statins; Diabetes; Insulin sensitivity; Glucogenesis

INTRODUCTION

Rate limiting enzyme of cholesterol synthesis pathway is HMG-CoA reductase (HMGCR), which converts HMG-CoA to mevalonic acid. When the activity of HMGCR is turned-down, the amount of cell-associated cholesterol is reduced, which activates SREBP-2-mediated signaling pathways. One of the important outcomes of SREBP-2 activation for cholesterol homeostasis is the upregulation of low-density lipoprotein (LDL) receptor (LDLR). The increased number of LDLR on hepatocytes enhances the removal of cholesterol-rich LDL particles from the blood circulation.[1] Currently, several HMGCR inhibitors (i.e. statins) are available and proved to be effective in reducing cardiovascular disease events but also in cardiac-related and overall mortality.[2] Such benefits of statins are believed to result from efficient removal of atherogenic lipoprotein particles, such as LDLs and intermediate density lipoproteins, from the blood circulation, which is represented by the reduction of LDL-cholesterol levels. Additionally, statins reduce the production of isoprenoid metabolites and such "beyond cholesterol" effects may also contribute to the prevention of cardiovascular disease. Statins are in general well-tolerated, but currently the concerns are raised if statins may increase the risk of new-onset diabetes mellitus (NOD).

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In this review, a number of possibilities implying statins' effects on glucose metabolism will be discussed. The clinical implications of statins to change glucose levels have been extensively described in previous studies. Therefore, this review will focus on the basic mechanisms by which statins affect the response of major organs involved in glucose metabolism.

LIVER

Glucose transporter

Unlike other cell types, hepatocytes are capable of gluconeogenesis and the need for glucose uptake is only modest. The role of hepatocytes to supply glucose and other carbohydrates for fuel is vital for cell survival, which involves a family of integral membrane glucose transporter (GLUT) molecules.[3] Of 14 members of GLUT family, GLUT-1, GLUT-2,[4] GLUT-9,[5] and GLUT-10,[6] have been documented on human hepatocytes but little is known about their extrahepatic expression or function. GLUT-2 is mainly distributed in the sinusoidal plasma membrane of hepatocytes and plays a major role in the glucose transport at Km of up to 66 mmol/L.[7] The transport of glucose via GLUT-2 is (should be) bi-directional, meaning GLUT-2-mediated glucose efflux from hepatocytes is essential for peripheral glucose supply under fasting glucose-depleted state.[8] Fraulob et al.[9] fed C57BL/6 mice a high fat diet and found that co-treatment with rosuvastatin (20 mg/kg/day) ameliorated insulin resistance and hepatic steatosis. Moreover, upregulation of GLUT-2 and SREBP-1c expressions in liver was not observed in statin-treated mice,[9] suggesting statin may not increase glucose overproduction or synthesis of triglyceride by liver. On the other hand, little has been studied if statins may change the expression levels of GLUT-2 by hepatocytes under euglycemic conditions. Since statins suppress isoprenoid/mevalonate pathway, it is possible that subsequent downregulation of small GTPases such as RhoA and Rab4 may slow down the traffics of hepatic GLUT-2 to the cell membrane as reported in the case of GLUT-4 in adipocytes and skeletal muscle. If this happens, the function of GLUT-2, i.e. glucose uptake under glucose-fed condition and glucose production and release under fasting and glucose-depleted conditions, could be jeopardized. However, little large-scale studies have been performed if statins may simultaneously induce fasting hypoglycemia and postprandial hyperglycemia.

Glucokinase

Glucokinase (GCK) converts glucose to glucose-1-phosphatate, which is a key substance for the subsequent glycolysis and gluconeogenesis. GCK shows a markedly lower affinity for glucose than other hexokinases and lacks of significant feedback inhibition, meaning the rate of GCK-dependent glucose phosphorylation is proportional to the glucose concentration in the normal physiological range.[10][11] A downstream GCK promoter in hepatocytes responds to insulin[12] and also requires the activation of SREBP-1c[13] and LXR-α,[14] i.e. the essential cell signalings for the production of triglyceride. Pramfalk et al.[15] analyzed human liver biopsy samples and found that the treatment of high-dose atorvastatin (80 mg/day for 4 weeks), which decreased both serum LDL-cholesterol and triglyceride levels, reduced mRNA expressions of GCK (50%) and SREBP-1c (30%) while glucose-6-phosphatase (90%) mRNA expression was upregulated. The study also showed the decrease in triglyceride content in liver after atorvastatin treatment without altering serum glucose or insulin levels.[15] These results suggest that statin's benefit on liver is the suppression of triglyceride synthesis and subsequent hepatic accumulation while the synthesis of glycogen is increased. However, serum glucose levels may be elevated due to GCK downregulation although glucose uptake by liver is relatively minor. In the other report, profound GCK overexpression (>6 fold) was

induced in rats, which showed the reduction of circulating glucose (38%) and insulin (67%) levels but also developed hypertriglyceridemia (190%) and free fatty acidemia (310%).[16] Taken together, the reduced expression of GCK under statin treatment can increase the chance of hyperglycemia, but also reduce the accumulation of glucose in hepatocyte and subsequent glycolysis and lipogenesis. It is questionable if the lowered GCK expression (up to 50%) observed in statin treatment could elevate serum glucose and insulin levels through less efficient hepatic glucose uptake. In human cases of heterozygotes GCK deficiency showing 50% of usual GCK activity, mild elevation of fasting glucose and HbA1C levels were observed.[17] Such reduced GCK activity could be comparable to the condition observed under high dose of statin treatment. However, the GCK activities in other tissue could also contribute to the elevation of glucose levels. In addition to lowered GCK expression, statins' another effect to upregulate glucose-6-phosphatase may increase de novo gluconeogenesis and subsequent glucose release.

The change of cholesterol content in hepatocytes by statin treatment had been discussed as a possible mechanism. The inhibition of HMGCR by statins results in the reduction of cholesterol synthesis. Hepatocytes show the highest expression level of LDLR, which is further upregulated under statin treatment through upregulation of SREBP-2. As a result, the enhanced LDLR-mediated uptake of LDL particles increases the accumulation of cytosolic cholesterol in hepatocytes. In other report, Schonewille et al.[18] suggested the different mechanism of cholesterol accumulation, in which male C57/BL6 mice fed 0.01% rosuvastatin, 0.05% atorvastatin or 0.2% lovastatin showed the actual increase in hepatic cholesterol synthesis by robust increase in the production of substrates for HMGCR and upregulations of cholesterol synthesis enzymes mevalonate kinase (Mvk), phosphomevalonate kinase (Pmvk), farnesyl-diphosphate farnesyltransferase 1 (Fdft1/Sqs), and squalene epoxidase (Sqle).[18] Both findings seem to be, at least for hepatocytes, reasonable explanations for the increased amount of cell-associated cholesterol under statin treatment. The negative regulation of hepatic GCK by hepatic cholesterol content is supported by a Tsai and Dyer's report,[19] in which cholesterol or cholic acid feeding to rats, which increased cholesterol content in the liver, developed depressed activities of GCK and glucose-6-phosphate dehydrogenase in the liver but not in the adipose tissue.

Insulin receptor
Insulin receptor (IR) signaling itself obviously affects cholesterol homeostasis in liver. Miao et al.[20] developed hepatic IR deficiency mice which showed decrease in expressions of SREBP-2 and cholesterologenic genes and these effects were not reversed by statins. These findings raise the possibility that insulin and/or IR signaling (e.g. mTORs) is required for hepatic cholesterol synthesis. Conversely, statin treatment affects the activity of hepatic IR. In animal models, statin treatment increases tyrosine phosphorylation in hepatic IR and insulin receptor substrate (IRS)-1/2, and serine phosphorylation of Akt (through PI3K).[21][22] Interestingly, these effects of statin were still observed in LDLR-deficient insulin-resistant mice even after mevalonate supplementation, suggesting the involvement of both intrinsic and extrinsic LDLR-dependent cholesterol homeostasis in hepatocytes is less likely.

Glucose production
Pregnane X receptor (PXR), activated by statins, binds and dephosphorylates serum/glucocorticoid regulated kinase 2 (SGK2). The PXR-SGK2 complex interacts with PXR-SGK2 response elements and an IR sequence region and eventually upregulate glucose-6-phosphatase.[23] The result may increase endogenous glucose production (EGP). However,

in vivo studies show that treating diabetic human subjects with atorvastatin (10 mg/day) or simvastatin (10 mg/day) resulted in only slight increase in EGP.[24][25] The upregulation of hepatic glucose-6-phosphatase by statin treatment has been reported in human as discussed above,[15] but detailed mechanism is not clear.

PANCREAS

Glucose transporter

The capability of insulin secretion from pancreas β cells is mandatory for maintaining euglycemic condition. The insulin secretion is the metabolic outcome of pancreas β cells in response to fuels, foremost glucose. Thus, type 2 diabetes mellitus (T2DM) can be developed due to dysfunctional "fuel"-stimulated insulin secretion. It is well known that glucose uptake can be through GLUTs, mostly through GLUT-1 to 4. Zhao and Zhao[26] treated human pancreas β cells with atorva-, rosuva-, prava-, and pitavastatin (up to 100 nM) and found that atorvastatin and pravastatin elicited a concentration-dependent inhibition of GLUT-2 expression in human pancreas islet β cells, while rosuvastatin and pitavastatin showed a slight increase in GLUT-2 expression. On the other hand, little had been studied if other GLUTs including GLUT-1 or GLUT-3 expressions by pancreatic beta cells are changed under statin treatment. The function of pancreatic GLUT-2 had been extensively studied in murine and rodent models, which is however known to be little expressed in human pancreas beta cells while GLUT-1 and GLUT-3 expressions are preserved. A previous histological analysis of human pancreas islets showed that GLUT-1 expression is dominant and did not significantly change in the context of the various (pre-) diabetic conditions including T2DM and islet autoantibody positive conditions.[27] Pancreas β cells must respond to the subtle change of extracellular glucose concentration through controlling insulin secretion. A kinetic study showed that glucose uptake via GLUT-1 seemed to be most sensitive, i.e. at least nine times higher than that of GLUT-2.[28] The Km value of glucose uptake via GLUT-1 in pancreas β cells is only 1–2 mmol/L, which could be ideal as a sensor for pancreas β cells to monitor circulating glucose levels. Therefore, more research about the relationship between GLUT-1 regulations in human pancreas β cells and statin treatment might be necessary in the future.

Glucokinase

The glucose in the cytosol of β cells is phosphorylated by GCK. Loss of function mutations, as reported in the case of maturity onset diabetes of the young 2, results in a right shift in the dose-response curves of glucose and insulin secretion while dysregulation of insulin secretion and degree of hyperglycemia do not seem to be progressive.[29] Little has been studied if statins may alter GCK expression levels in pancreas β cells. Zhang et al.[30] found that HMGCR inhibition (ex vivo) of pancreatic beta cells isolated from streptozotocin-induced diabetic mice showed decrease in the amount of cell-associated cholesterol content and increased mRNA expression of GCK. Hao et al.[31] tested apoE-KO or/and ob/ob mice with C57BL/6J background. Insulin secretion from pancreatic islets and pancreas GCK activity was inversely correlated with cholesterol contents associated with islets. Moreover, cholesterol depletion and enhanced insulin secretion in islets were observed after treatment with mevastatin.[31] Such changes were accompanied by upregulation of insulin-1 (INS-1), insulin-2, pancreatic and duodenal homeobox factor-1 (PDX-1) transcripts,[30] suggesting reduced cholesterol burden in islets through statin treatment showed enhanced insulin synthesis for the secretion as well as glucose sensing. Therefore, one of the fundamental questions regarding the change of regulation of pancreas β cells under statin treatment is if there would be any change of

cell-associated cholesterol content. Theoretically, statin may decrease cell-associated cholesterol content through the inhibition of HMGCR and subsequent cholesterol synthesis. On the other hand, statin may increase cell-associated cholesterol content if activated SREBP-2 signalings upregulates LDLR. However, it is unlikely because LDLR protein is hardly expressed in pancreas though LDLR transcripts are detected in virtually all cell types.[32]

Insulin synthesis and secretion

Glucose-6-phosphate generated by GCK is eventually changed to pyruvate, which is a representative substrate for the generation of ATP in mitochondria. Although such glycolytic metabolism is tightly coupled to mitochondrial metabolism, other potential substrates can also trigger TCA cycle (i.e. exogenous pyruvate or glutamate), and might cause hyperinsulinism. The other pentose phosphate pathway is purely cytosolic and eventually generates nicotinamide adenine dinucleotide phosphate (NADPH), alters redox potential and reduces insulin secretion, but these could be minor for controlling de novo insulin secretion.[33] The series of cascade metabolic pathway changes mitochondrial plasma membrane electrical potential oscillations. The changes of mitochondrial membrane potential cause the inhibition of K_{ATP}-channels, which in turn induces transient opening of voltage-activated Ca^{2+} channels and subsequent insulin secretion.[29][34]

Under (pre)diabetic conditions, mitochondrial mass is increased (up to 60%) while the number shows little change. Activities of a number of metabolic enzymes such as glycerol phosphate dehydrogenase, pyruvate carboxylase, succinyl-CoA:3-ketoacid-CoA transferase and FAD-linked glycerol phosphate dehydrogenase were reduced in human β cells under diabetic conditions.[35][36] However, it is not studied if statins may change those enzyme activities or expression levels. Additionally, the increased expression of uncoupling protein 2 (UCP2), which could uncouple the respiratory chain from ATP production, has been described as a cause of mitochondrial dysfunction in diabetic patients.[37][38] Atorvastatin (10 umol/L) reportedly decreased UCP2 expression in rat primarily cultured cardiomyocytes, which enhanced energy metabolism and myocardial remodeling.[39] On the contrary, co-incubation of New Zealand rabbit cardiomyocytes with rosuvastatin (1 uM) under ischemia/reperfusion model enhanced UCP2 expression while series of pro-apoptotic and pro-oxidant genes were suppressed.[40] Cautious interpretation may be necessary if such opposite changes of UCP2 expression suggest the 'restoration' of mitochondrial function. The other study tested human pancreas islet cells and rat-insulin secreting INS-1 cells and demonstrated that atorvastatin (100 ng/mL) but not pravastatin attenuated insulin secretion under high glucose concentration and these finding is thought to be due to decreased functions of complex I, III, IV, and V and lowered co-enzyme Q10 protein.[41] Yaluri et al.[42] treated mouse pancreatic MIN6 β cells with either 14.3 uM simvastatin or 26.3 uM pravastatin and found that only simvastatin reduced insulin secretion through affecting K_{ATP} and Ca^{2+} channels and these effects were restored by direct activation of cAMP-dependent signaling and GLP-1 receptor stimulation. The other study measured insulin secretion using INS-1 832/13 cells, which was increased by rosuvastatin (20 nM–20 uM) under euglycemic condition (2.8 mM) but decreased under hyperglycemia (16.7 mM). Downstream of K_{ATP} channel and Ca^{2+} channel was not affected by rosuvastatin except maximal concentration tested (20 uM) under hyperglycemia.[43] The statins' proposed effect to enhance upstream GCK expression as discussed above may aggravate the condition of the increased basal and fasting insulin secretion. The uncoupling process and reduced ATP production in mitochondria are increased under hyperglycemia, which can be more exaggerated by more limited supply of isoprenoids and co-enzyme Q10 protein under statin medication. Oral supplementation of co-enzyme Q10 has been described

as beneficial for enhancing mitochondrial ATP production, but more evidences are needed if oral delivery can actually increase tissue level (i.e. pancreatic beta cells) of co-enzyme Q10.[44] Hyperglycemic condition is also associated with the increased NADH and the inhibition of electron transport at complex III. Co-enzyme Q10 supplement may inadvertently increase oxygen free radical (i.e. superoxide) generation unless other uncoupling conditions are simultaneously resolved.[45]

Islets survival and apoptosis

The apoptosis of β cells is induced by hyperglycemia, which is determined by the balance of pro- and anti-apoptotic cell signaling.[46] It is highly controversial whether statins affect pancreas β cells' survival. Atorvastatin (25–125 uM) increased reactive oxygen species production and mitochondria-mediated apoptosis in rat islets.[47] On the other hand, atorvastatin treatment (30 mg/kg/day) to C57BL/6J mice showed the preservation of β cell mass and sensitivity of insulin secretion, which involved upregulation of PDX-1 and downregulation of activating transcription factor 4 (ATF4; ER stress marker), CCAAT-enhancer-binding protein homologous protein, and phosphorylated eukaryotic initiation factor 2α.[48] Long-term pravastatin treatment (0.05%) to OLETF rats showed decreased serum glucose concentration and fibrotic area, elevated superoxide dismutase activity and down-regulated transforming growth factor-β1 mRNA in the pancreas.[49] On the contrary, long term pravastatin (40 mg/kg/day) treatment to LDLR-deficient mice showed reductions of exocytosis-related SNARE proteins (SNAP25, Syntaxin 1A, VAMP2) and increased apoptosis markers (Bax/Bcl2 protein ratio, cleaved caspase-3 and lower NAD[P]H production rates) in pancreatic islets, suggesting the reduction of insulin exocytosis and the increased β cell death.[50] Simvastatin,[51] atorvastatin,[52] and pravastatin[53] reportedly induce anti-apoptotic Akt signalings. But other results showed the inhibition of p-Akt by atorvastatin, pravastatin, and rosuvastatin.[26] Taken together, multiple factors including dose of statin, glycemic condition, concentration of cholesterol etc. can affect the outcome of the experimental study and it is largely unknown if conventional dose of statins may affect β cells' longevity in human.

ADIPOCYTES AND MUSCLE

Insulin receptor signalings

Insulin receptor (IR) is a tyrosine kinase receptor. Tyrosine residues in agonist(insulin)-bound IR is phosphorylated and then binds to series of IRS1–4, which trigger multiple cell functions including glucose uptake through GLUT-4.[54] Jiang et.al. treated rat cardiomyocytes with either atorva-, prava- or rosuvastatin (up to 10 uM) and found that only atorvastatin decreased glucose uptake and expressions of GLUT-4 and IRS-1 while RhoA protein expression showed no change.[55] Other studies using simvastatin (5 uM) showed the suppression of the phosphorylation of IR, IRS-1 and Akt, and total expression of IR, IRS-1 or glycogen synthase kinase 3β (GSK-3β), but not Akt, in L6 skeletal muscle myotubes and C2C12 myotubes.[56][57] In case of adipocytes, 3T3-L1 cultured adipocytes had been extensively used and shows the trend that hydrophobic rather than hydrophilic statins reduced phosphorylation of IRS-1 and Akt, and expressions of small GTPases such as RhoA and Rab4 which are required for traffic of GLU-4 to the cell membrane.[58][59] Therefore, less generation of isoprenoid metabolites due to statin treatment may possibly inhibit IRS-derived signaling and the translocation of GLUT-4 to cell membrane. However, it should be noted that these such suppressive changes may become more evident for any statins with high lipophilicity under higher concentration levels in in vitro experimental settings.

Unlike in vitro results, the series of earlier in vivo animal studies suggest the opposite outcomes after statin treatment. Wistar rats fed high fat diet with/without lovastatin (4 mg/kg/day) and showed that skeletal muscle from lovastatin-treated rats showed the enhanced insulin-stimulated IRS-1/phosphatidylinositol 3-kinase/Akt pathway in parallel with a decrease in the inflammatory pathway (c-jun N-terminal kinase and I κB kinase/inhibitor of κB/nuclear factor κB) related to insulin resistance.[22] Other animal study using fructose-fed hamsters and rosuvastatin (10 mg/kg/day) showed similar findings, in which rosuvastatin showed significant increases in tyrosine-phosphorylation of the IR and IRS-1 in liver, muscle and adipose tissue.[21] FVB mice fed high fat diet and simvastatin (40 mg/kg/day) showed higher adiponectin levels.[60] These results suggest that the advanced hypercholesterolemic condition itself could deteriorate insulin sensitivity, which could be, at least in part, 'normalized' by statin treatment.

Fatty acid metabolism

While statins' effects to reduce cholesterol and triglyceride have been well established, few studies had been performed to investigate the change of free fatty acid (FFA) metabolism under statin treatment. In a recent meta-analysis, both groups with atorvastatin and simvastatin medications showed the reduction of plasma FFA concentration (−19.42%).[61] The release of FFA from adipocytes is due to lipolysis and is increased under insulin resistance. Atorvastatin treatment (up to 80 mg/day) to diabetic subjects dose-dependently decreased activity of hepatic lipase, which is responsible for lipolysis from adipocytes,[62] suggesting statin may inhibit lipotoxicity due to hyperFFAemia under diabetic condition. Moreover, activities of lipoprotein lipase (LPL), which delivers FFA to peripheral tissue, are reportedly enhanced by atorvastatin (1–10 uM)[63]64) and pitavastatin (1 uM)[64] in 3T3-L1 preadipocytes and L6 skeletal muscle cells, respectively, probably through phosphorylation of adenosine monophosphate-activated protein kinase. These findings suggest that statin may reduce plasma FFA levels especially under diabetic condition. Although above findings may contribute to the clearance of circulating FFA, excess accumulation of FFA in skeletal muscle can inhibit glucose uptake through GLUTs and its further utilization[65] and this could be predisposed by increased de novo fatty acid synthesis under statin treatment. Treatment with lovastatin (10 uM)[66] or depletion of mevalonates and farnesyl pyrophosphate[67] increased FFA synthesis in keratinocytes and CaCo-2 colon epithelial cells, respectively, under sterol depletion through upregulation of fatty acid synthase. The other study showed the decreased LPL activity in THP-1 cultured monocytes and prevented the transformation into foam cells by simvastatin and atorvastatin (up to 20 uM), suggesting statins' effect on LPL could be cell-specific.

Adipocytes or adipose tissue?

It is controversial if statin may change the level of adiponectin. A series of meta-analysis shows that long-term statin (> 12 weeks; atorvastatin, simvastatin, rosuvastatin, pravastatin or pitavastatin) medication to human increased adiponectin level by 0.88 μg/mL[68] while leptin,[69] resistin and visfatin[70] levels showed no significant changes. In small-scale clinical studies or in vitro experimental studies, circulating levels or mRNA/protein expression levels of leptin show the tendency of reduction by statins. For example, both atorvastatin (1–10 uM) and simvastatin (1 uM) decrease leptin and monocyte chemoattractant protein-1 (MCP1) expressions in human white adipocytes.[71] The elevation of adiponectin and reduction of leptin suggest the favorable effect of statin to prevent atherogenesis. But such changes of adipokines were not always associated with the improvement of insulin sensitivity in adipocytes.

The adipose tissue also contains adipose tissue macrophages, which may influence the functional status of adipocytes. Kralova et al.[72] analyzed the characteristics of macrophages in visceral adipose tissue and the proportion of pro-inflammatory (CD14^{+} CD16^{+} CD36^{high}) macrophages was higher in hypercholesterolemia and lower in statin-treated groups, respectively. Abe et al.[73] treated ob/ob mice with 0.05% pravastatin and 0.003% pitavastatin and found the attenuation of the induction of pro-inflammatory genes (i.e. TNF-α, IL-6, and MCP1) in adipose tissue. In in vitro conditions, TLR4- or TLR3-stimulated macrophages elicited the similar pattern of response.[73]

Recently, the association of inflammasome such as NOD-like receptors pyrin domain containing 3 (NLRP3) with statin-induced diabetes has been raised. Statins have been shown to induce the formation of NLRP3, which in turn activates caspase-1/IL-1β pathway in macrophages only in the presence of LPS.[74][75] On the contrary, other research groups describe statin inhibits the formation of NLRP3 in immune and vascular cells in various inflammatory and oxidative conditions.[76-81] Up to date, none of studies prove the statin-stimulated NLRP3 formation in adipose tissue in vivo. Moreover, the role of NLRP3 in other tissues involved with glucose metabolism has not been studied. It remains to be a hypothesis that, especially in obese conditions, NLRP3-induced IL-1β formation in adipose tissue is possible and may aggravate the pre-existing insulin resistance.

SUMMARY AND CONCLUSION

A number of experimental findings strongly suggest that statins regulate both glucose and cholesterol homeostasis. The initial change of cell signalings elicited by statins is not different from specific cell types or tissues (i.e. less production of isoprenoid metabolites) and the depletion of cell-associated cholesterol content. Relatively lipophilic statins are described as more diabetogenic in many in vitro studies, which are probably because they can diffuse more easily into cells under culture conditions and the inhibition of the production of isoprenoids becomes more potent. Moreover, many of these results are found at relatively high concentration of statins. This may not only result in general decrease in cellular function but also induce cell apoptosis. It should be considered that in vivo concentrations of statins in specific tissue are affected by multiple factors such as bioavailability, gastrointestinal absorption, and hepatic uptake etc. as well as solubility itself.[82]

Moreover, it is confusing whether the final outcome of cell-associated cholesterol level becomes increased or decreased by statin treatment. Interestingly, both opposite changes have been described as the cause of dysregulation of glucose metabolism under statin treatment. That might be due to initial depletion of cell-associated cholesterol, which is then "over-compensated" by LDL uptake through SREBP-2-mediated upregulation of LDLR and probably through the upregulation of cholesterologenic genes. In fact, results of in vitro experiments using either cholesterol depletion or cholesterol loading have been extrapolated to the effect of statins. LDLR expression level could be very different from specific tissues. Hepatocytes abundantly express LDLR, of which expression level is far lower in other cells such as pancreas islet cells and adipocytes. Moreover, it is not clear whether LDLR upregulation under statin treatment results in "overload" or "normalization" of cell-associated cholesterol content.

On the other hand, a series of in vivo results show statin treatment to rats or mice resulted in the reduction of glucose levels with improvement of insulin sensitivity and these findings became more evident under hypercholesterolemic and hyperglycemic condition. However, such findings favorable to statins may not be totally due to statins' pharmacological action, because statin-treated animals usually showed less gain-of-weight. Moreover, the dose of administered statins is still debatable. Recently, another cholesterol lowering drug had been developed, i.e. PCSK9 inhibitor. Its role is to enhance LDLR recycling and further reduce circulating cholesterol levels through more efficient LDL uptake. The circulating cholesterol level will become extremely-lowered. Any cells which abundantly express LDLR may have more cell-associated cholesterol while the other cells with little LDLR show more advanced cholesterol depletion. If tissues such as pancreas islets, adipocytes and skeletal muscle do not respond to PCSK9 inhibition, unlike hepatocytes, the cell-associated cholesterol levels will become more depleted. Therefore, in order to resolve cholesterol issue in the development of NOD, it would be very interesting to evaluate the change of glucose regulation in specific tissues under PCSK9 inhibition or other types of pharmacological intervention with or without statins, which may also provide information if statins are truly diabetogenic.

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