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Could changes in adiponectin drive the effect of statins on the risk of new-onset diabetes? The case of pitavastatin

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Abstract

Statins represent the elective lipid-lowering strategy in hyperlipidemic and high cardiovascular-risk patients. Despite excellent safety and tolerability, reversible muscle-related and dose-dependent adverse events may decrease a patient's compliance. Large meta-analyses, post-hoc and genetic studies showed that statins might increase the risk of new-onset diabetes (NOD), particularly in insulin-resistant, obese, old patients. Race, gender, concomitant medication, dose and treatment duration may also contribute to this effect. Based on this evidence, to warn against the possibility of statin-induced NOD or worsening glycemic control in patients with already established diabetes, FDA and EMA changed the labels of all the available statins in the USA and Europe. Recent meta-analyses and retrospective studies demonstrated that statins' diabetogenicity is a dose-related class effect, but the mechanism(s) is not understood. Among statins, only pravastatin and pitavastatin do not deteriorate glycemic parameters in patients with and without type 2 diabetes mellitus. Interestingly, available data, obtained in small-scale, retrospective or single-center clinical studies, document that pitavastatin, while ameliorating lipid profile, seems protective against NOD. Beyond differences in pharmacokinetics between pitavastatin and the other statins (higher oral bioavailability, lower hepatic uptake), its consistent increases in plasma adiponectin documented in clinical studies may be causally connected with its effect on glucose metabolism. Adiponectin is a protein with antiatherosclerotic, anti-inflammatory and antidiabetogenic properties exerted on liver, skeletal muscle, adipose tissue and pancreatic beta cells. Further studies are required to confirm this unique property of pitavastatin and to understand the mechanism(s) leading to this effect.

Keywords: Statins; Type 2 diabetes mellitus (T2DM); Insulin sensitivity; Pitavastatin; Adiponectin

1. Statins and type 2 diabetes mellitus: the state of the art

Several randomized-controlled trials have demonstrated the benefits of lowering low-density-lipoprotein cholesterol (LDL-C) with statins to reduce cardiovascular (CV) risk in a wide range of populations, including patients with type 2 diabetes mellitus (T2DM) [1–3]. Although statins are safe, recent studies highlighted the possibility that they may cause the development of new-onset diabetes (NOD) [4–6]; however, this small risk varies with the baseline risk of developing T2DM [6].

While atorvastatin, simvastatin, rosuvastatin, lovastatin and fluvastatin generally deteriorate glycemic parameters in patients with and without T2DM, pravastatin and pitavastatin seem neutral [6]. The earliest evidence on these differences comes from a post-hoc data analysis from the Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction (PROVE-IT) 22 trial, where 3,382 patients without T2DM showed 0.30% and 0.12% increase from baseline in glycated hemoglobin (HbA1c) with atorvastatin 80 mg and pravastatin 40 mg, respectively [7]. To investigate statin-induced risk of developing T2DM, Sattar et al. [5] performed a meta-analysis of 13 trials including 91,140 patients without T2DM. Overall, standard-dose statin was associated with a 9% increased risk for T2DM over 4 years, with little heterogeneity between trials. To corroborate this evidence, later, a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial (N = 3,803) showed that NOD developed in 166 of 1,905 patients randomized to atorvastatin 80 mg/day and in 115 of 1,898 subjects of the placebo group (8.71% vs. 6.06%) [8]. The Canadian Network for Observational Drug Effect Studies Investigators [9] study and a meta-analysis performed by Preiss et al. [4] on data from five trials in which 32,752 participants without baseline T2DM received intensive- versus standard-dose statin, documented that among statins, those with

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higher potency are more likely to increase the risk of NOD. Moreover, these effects seem to be dose-related [4]. NOD, which is more evident in patients with pre-existing T2DM risk factors [8], elderly [5], women [10] and Asians [11,12], is a cause for concern because long-term T2DM is associated with a 2-fold increased CV risk [13,14]. Based on this evidence, FDA changed the labels of all the available statins (pravastatin and pitavastatin included) and of statin-containing combinations in the USA, including warnings about the possibility of increased glycemia and HbA1c, while EMA included the warning in the product information of all the statins authorised in the European Union and issued guidance on an increased T2DM risk.

2. Is statin-induced risk of NOD a class effect?

Retrospective studies and a recent meta-analysis conducted on 246,955 patients from 135 randomized-controlled trials confirmed that statins increase T2DM risk, but no statistical difference was seen among drugs and doses [12,15]. A population-based cohort study performed in 471,250 Canadians without T2DM showed that patients taking atorvastatin, simvastatin or rosuvastatin had an increased risk of developing T2DM versus pravastatin, fluvastatin and lovastatin-treated patients and the order of diabetogenicity was the same, regardless which statin was used for primary or secondary prevention. Although similar results were observed when grouping statins by potency, the risk of incident T2DM associated with rosuvastatin became non-significant when the dose was taken into account [16]. Nevertheless, all these results require confirmation in large-scale, head-to-head clinical trials, since most of these studies did not systematically assess T2DM incidence, were underpowered to detect differences between statins, and were retrospective [6].

Very recently, utilizing data from 20 randomized-controlled trials, Swerdlow et al. [17] not only further documented the increased risk (odds ratio 1.12) of statin-induced NOD, but also tried to understand the mechanism(s) of this effect, using a genetic approach. When they studied single-nucleotide polymorphisms (SNPs) near the gene encoding for the 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, previously demonstrated to be associated with changes in LDL-C and evaluated their relationship with waist circumference, body weight, body mass index (BMI), insulinemia, glycemia and risk of T2DM, a slight but significant increased risk of T2DM emerged. Interestingly, since this effect is associated with an on-target reduction in HMG-CoA activity, it implies that the risk of NOD cannot be modified or avoided by new and more specific statins [17]. Moreover, the documented association with BMI may suggest a mechanism downstream of HMG-CoA reductase inhibition, by which increased body weight may increase insulin resistance and diabetes. In fact, among the several hypotheses raised, increases in caloric and fat intake during statin treatment have been related to the onset of NOD [18]. Nevertheless, it has to be underlined that the magnitude of the effect on caloric intake and BMI seems insufficient to account for the increased risk of T2DM; moreover, this effect is not dose-related, differently from statin-induced NOD [17,19]. A recent interesting study demonstrated that the prevalence of NOD is significantly lower in patients affected by familial hypercholesterolemia (n = 14,296) vs their unaffected relatives (n = 24,684) (odds ratio 0.35 and 0.51 respectively for LDL-receptor-negative and LDL-receptor-defective mutations) [20]. Two major explanations have been proposed. The first, always connected to calories retention, suggests that these patients are more willing to follow lifestyle measures, thus contributing to decrease the risk of NOD. The second relies on the fact that these patients may experience a possible lack in activation of Sterol Regulatory Element Binding Proteins (SREBPs), a fundamental step in the mechanism of LDL-receptor increase [18]. In fact, statins increase LDL-receptor expression through activation of SREBP-1a, -1c and -2, which are also causally related to insulin resistance [21]. If true, this may explain why the more potent is the statin, the greater are the possible increase in SREBPs and LDL receptors, as well as reduction in plasma LDL-C and a higher incidence of NOD.

3. Mechanism of NOD: the role of adiponectin

To understand the mechanism(s) underlying statin-induced NOD, several hypotheses have been raised [22–25]. Differences in lipophilicity, effects on calcium channels in β-cells, translocation of GLUT-4 transporter, decreases in ubiquinones, isoprenoids, dolichols, intracellular insulin signal transduction pathways, inhibition of adipocyte differentiation, adiponectin production/secretion and altered lipoprotein metabolism are the most frequently debated, but none of these has been fully convincing. The effects of statins on glucose in experimental models have been extensively reviewed by Koh et al. [26] and, more recently, by Brault et al. [23]. Many of these hypotheses rely on effects that have been demonstrated in *in-vitro* or *in-vivo* experiments, under conditions and at concentrations too far away from the clinical setting, with the result that several of them have not been confirmed in humans.

An interesting, very recent hypothesis has been raised by Henriksbo et al. [27]. Fluvastatin, simvastatin, lovastatin and atorvastatin dose-dependently increase the secretion of the proinflammatory cytokine interleukin-1b (IL-1b) in macrophages, an event that requires caspase-1 activity and priming with an immunogenic agent (e.g. LPS). This phenomenon indicates the activation of the inflammasome containing the pattern recognition receptors (PRR), NOD-like receptor family, pyrin domain containing 3 (NLRP3)/caspase-1, which have been demonstrated to correlate with the development of insulin resistance in rodents [28]. In obese mice, the impaired insulin-stimulated glucose uptake in adipose tissue by long-term fluvastatin treatment is

dependent on the NLRP3 inflammasome. Fluvastatin acts through the NLRP3/caspase-1 inflammasome in metabolic and immune cells of adipose tissue (which contains endogenous inflammasome-priming signals such as saturated fatty acids, ceramides, products of hypoxic and necrotic fat cells) and this mechanism may contribute to the development of T2DM. The clinical relevance is supported by the fact that subjects with metabolic syndrome have increased activation of the NLRP3 inflammasome in adipose-tissue macrophages and that T2DM patients present elevated inflammasome proteins NLRP3 and increased caspase-1 activation before being treated [19,29,30]. It is worthwhile to remind that activation of the NLRP3 inflammasome may be tissue- and statin-specific: therefore this effect may be not exerted by all statins and in all different populations. Even though clinical studies with different statins are required to further understand the mechanisms underlying the activation of the inflammasome, adipose tissue seems deeply involved in these mechanisms. The analysis of the effects of statins on adiponectin, a protein that is secreted only by adipose tissue and that plays anti-inflammatory and antidiabetic roles, may help to comprehend the molecular driver of this mechanism.

4. Clinical data assessing the beneficial effects of pitavastatin on NOD

As previously mentioned, among the available statins, pitavastatin seems neutral, if not beneficial, for biomarkers of glucose metabolism, in T2DM and dyslipidemic patients, as demonstrated by clinical trials and/or retrospective studies [31]. In the CHIBA-Study subanalysis of diabetic patients, atorvastatin 10 mg/day but not pitavastatin 2 mg/day significantly increased glycoalbumin. Pitavastatin had no significant influence on fasting plasma glucose, HbA1c, insulin or homeostatic model assessment (HOMA-IR). In another retrospective analysis, atorvastatin 10 mg/day, but neither pravastatin 10 mg/day nor pitavastatin 2 mg/day, significantly increased plasma glucose and HbA1c [32]. In the LIVES study, pitavastatin significantly decreased HbA1c in diabetic patients [33], even if on top of antidiabetic therapy [34].

Finally, the large-scale Japan Prevention Trial of Diabetes by Pitavastatin in Patients with Impaired Glucose Tolerance (J-PREDICT) has been designed specifically to investigate pitavastatin's effect on T2DM [35]. Preliminary results show that lifestyle modification plus 1–2 mg/day of the statin significantly reduced the cumulative incidence of T2DM in 1,269 high-risk patients with impaired glucose tolerance, compared to lifestyle modifications alone [36,37] (Fig. 1).

In Table 1 we collected 31 clinical trials (where pitavastatin was used alone or "head to head" with other statins) reporting the effects of pitavastatin on glycemia and insulinemia. Among the 18 studies in which only pitavastatin was utilized, it did not alter these two parameters in 15 studies, and even ameliorated them in 2. In only one

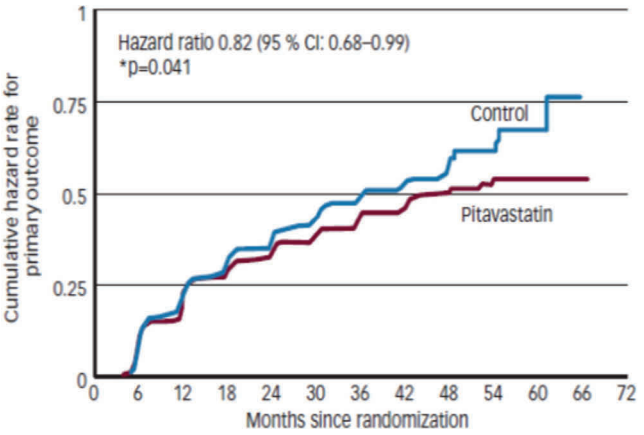

Fig. 1. Pitavastatin is associated with a lower incidence of diabetes in Japanese patients with impaired glucose tolerance. Preliminary data from the J-PREDICT study. From Odawara et al. [37], 73rd American Diabetes Association, 2013.

study the use of the statin paralleled with a deterioration of HbA1c [56]. In 6 of the 13 "head to head" studies, pitavastatin was significantly better than the comparator (pravastatin, rosuvastatin, atorvastatin, simvastatin), while in the remaining six it was considered equivalent. Altogether, the drug seems not to alter insulin resistance and not to interfere with insulin synthesis and secretion. These considerations support the hypothesis of a neutral or beneficial effect of pitavastatin on glucose homeostasis. The recent study by Cho et al. [67] is the only one documenting glucose deterioration and incidence of NOD by pitavastatin. Cho et al. retrospectively enrolled consecutive 3,680 patients without T2DM or impaired fasting glucose who started receiving a statin to lower their cholesterol and evaluated the incidence of NOD according to the statin used for a mean duration of 62.6±15.3 months. Pitavastatin showed the strongest incidence (7.8%) of the development of NOD, followed by rosuvastatin (6.5%) and pravastatin (5.8%), while simvastatin (3.4%) seemed the most protective. As reported by Cho et al., lack of data on compliance, statin dosage and adherence, different numerosity among cohorts, differences in patients' baseline characteristics, but mostly the fact that the newest pitavastatin may have been administered to patients at higher risk of diabetes, suggest caution in the interpretation of these results.

Based on these premises, it is of interest to understand whether pitavastatin is "different" from the other statins regarding NOD and glucose metabolism. In particular,

1. **its pharmacological profile** and
2. **its effect on adiponectin in clinical studies**

may unravel the mechanisms underlying the beneficial or neutral effect on NOD documented in clinical studies.

4.1. Pitavastatin's pharmacological profile

Thanks to their HMG-like moiety, statins are selective and potent HMG-CoA reductase inhibitors, they do not show relevant affinity toward other enzymes or receptors [68], and their effects are strongly related to their target site of action.

Table 1
Clinical trials reporting the effects of pitavastatin on glucose metabolism

First author [ref.]	Population	Effect on glucose/insulin	Effect on lipids or other parameters
Sone [38]	33 T2DM patients.	No significant increases in FPG.	Decrease in TC, LDL-C and TG; increase in HDL-C.
Kawai [39]	79 T2DM patients.	No effect both on FPG and HbA1c.	Decrease in LDL-C and TG.
Tokuno [40]	72 T2DM and hyperlipidemic patients.	Pitavastatin or fenofibrate had no effect both on FPG and HbA1c.	Decrease in LDL-C and TG.
Yamakawa [32]	T2DM patients treated with pitavastatin (n = 95), atorvastatin (n = 99) or pravastatin (n = 85).	Pitavastatin and pravastatin, but not atorvastatin had no effect both on FPG and HbA1c.	Decrease in TC. Atorvastatin and pravastatin lowered LDL-C.
Nomura [41]	64 T2DM patients.	No effect on HbA1c.	Decrease in TC, LDL-C and TG; increase in HDL-C. Increase in adiponectin.
Matsumoto [42]	25 HC patients.	No changes in FBG, HbA1c.	Decrease in TC, LDL-C and TG.
Kono [43]	94 patients with coronary artery disease.	No changes in glucose levels.	No changes in cholesterol; improvements in peripheral microvascular function.
Lee [44]	100 elderly T2DM patients.	No effect on HbA1c.	Decrease in TC, LDL-C and TG; increase in HDL-C.
Arao [45]	16 patients with coronary artery disease.	No effect both on FPG and HbA1c.	Improved fasting and postprandial dyslipidemia; reduced oxidative stress and increased adiponectin.
Hounslow [46]	164 hyperlipidemic patients.	No clinically relevant changes in FPG, HbA1c, fasting insulin, HOMA-IR.	–
Mao [47]	55 T2DM and HC patients.	No effect both on FPG and HbA1c.	Decrease in TC, LDL-C and TG
Eriksson [48]	330 patients with HC or with combined dyslipidemia and at least two CV risk factors.	Pitavastatin: no change in FPG (12–56 weeks); Simvastatin: no change in FPG at 12 weeks; significant increase at 56 weeks.	Pitavastatin significantly increased HDL-C, simvastatin decreased TG.
Gumprecht [49]	Patients with T2DM and mixed dyslipidemia. Treatments for 12 and 56 weeks.	Week 12/56: atorvastatin (n = 141/64) increased FBG (+7.2%/7.3%). Pitavastatin: no effect both at 12 and 56 weeks.	Reductions in LDL-C and in non-HDL-C not significantly different between pitavastatin (−41%) and atorvastatin (−43%).
Yokote [50]	45 Japanese HC patients.	Atorvastatin increased glycoalbumin. Pitavastatin tended to be safer vs atorvastatin on all glycemic parameters.	–
Kato [51]	48 patients with T2DM, metabolic syndrome and hyperlipidemia.	No alterations in HbA1c.	Reductions in LDL-C and TG.
Liu [52]	225 Taiwanese high-risk HC patients	Atorvastatin (n = 113) significantly increased HbA1c vs pitavastatin (n = 112)	Pitavastatin 2 mg/day is equivalent to atorvastatin 10 mg in lowering LDL-C.
Shimabukuro [53]	31 T2DM HC and/or hyperTG patients.	pitavastatin 2 mg (n = 16) or atorvastatin 10 mg (n = 15). No significant differences in HbA1c (%), 6.60–6.80 pitavastatin vs 6.60–6.70 atorvastatin; HbA1c (mmol/mol), 49–51 pitavastatin vs 49–50 atorvastatin; FPG (mmol/l), 6.83–8.18 pitavastatin vs 6.78–6.66 atorvastatin.	Only pitavastatin increased cholesterol of medium HDL subclass. Serum TG and TG content in VLDL and LDL decreased by atorvastatin.
Yanagi [54]	90 T2DM patients.	No effect on glucose metabolism.	Decrease in LDL-C and TG; increase in HDL-C
Hiro [55]	252 patients with acute coronary syndrome (with/without T2DM)	Pitavastatin or atorvastatin did not alter % HbA1c (from 7.3 to 6.8 in T2DM and from 5.4 to 5.6 in non T2DM).	–
Motomura [56]	65 Japanese T2DM patients.	Increase in % HbA1c (from 6.8 to 7.1), no changes in FPG.	Decrease in TC, LDL-C and TG; increase in HDL-C
Yokote [57]	20,000 Japanese HC patients.	Pitavastatin did not affect HbA1c.	Pitavastatin significantly decreased LDL-C and elevated HDL-C.
Koshiyama [58]	178 Japanese HC patients, including 103 with T2DM.	Pitavastatin did not change HbA1c levels of diabetic patients.	Decreases in LDL-C and TG; increases in HDL-C.
Sasaki [59]	173 patients with LDL-C > 140 mg/dL and glucose intolerance.	Pitavastatin 2 mg/day or atorvastatin 10 mg/day did not significantly affect glucose metabolism.	Greater % change in HDL-C, apoAI, LDL-C, apoB, apoE and non-HDL-C with pitavastatin
Kurogi [60]	129 patients with coronary artery disease, HDL-C < 50 mg/dl and HC.	Pitavastatin 2–4 mg/day or atorvastatin 10–20 mg/day had no significant effect on HbA1c.	Beneficial effects of pitavastatin on HDL-C, apoAI and adiponectin greater than those of atorvastatin.
Han [61]	189 HC patients with high transaminases (ALT).	Pitavastatin and atorvastatin did not change plasma glucose.	Both decreased LDL-C and ALT.

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Table 1
(*continued*)

First author [ref.]	Population	Effect on glucose/insulin	Effect on lipids or other parameters
Saku [62]	295 patients with coronary artery disease and elevated LDL-C.	Atorvastatin and rosuvastatin, but not pitavastatin, increased HbA1c.	The three statins equally reduced LDL-C and LDL particles.
Chapman [63]	26 T2DM patients.	No significant differences in HbA1c, insulin, HOMA-IR after pitavastatin (n = 12); small (4%) increase in FPG at day 180. Similar results after pravastatin (n = 14).	Reduction in atherogenic lipoproteins.
Teramoto [33]	308 Japanese T2DM patients.	In the time-course analysis, HbA1c gradually decreased by 0.28% over the 104 weeks.	Decrease in LDL-C and TG; increase in HDL-C.
Kakuda [64]	10 Japanese healthy men.	After 4 weeks, pitavastatin 2 mg/day decreased insulinemia. After a test meal, glucose and insulin did not change	General improvement of lipid and oxidative parameters.
Mita [65]	28 T2DM, HC patients.	Pitavastatin had a more favorable effect on glycemic control (HbA1c, fasting glucose, HOMA-IR) than atorvastatin.	Effects were significantly different despite same LDL-C control
Daido [66]	86 Japanese T2DM and HC patients.	Pitavastatin 2 mg/day for 12 months did not alter glucose metabolism. FBG decreased in those with BMI > 25 kg/m^2	No changes in lipid-related values and no side effects.

BMI, body mass index; CAD, coronary artery disease; CHD, coronary heart disease; CRP, C-reactive protein; CV, cardiovascular; EPA, eicosapentaenoic acid; FBG, fasting blood glucose; FCHL, familial combined hyperlipidemia; FMD, flow-mediated dilation; FPG, fasting plasma glucose; GGT, gamma glutamyl-transferase; HC, hypercholesterolemic; HDL-C, high-density-lipoprotein cholesterol; HMW, high-molecular-weight; HOMA-IR, homeostatic model assessment of insulin resistance; HTG, high triglyceridemia; HbA1c, glycated hemoglobin; IGT, impaired glucose tolerance; IMT, intima-media thickness; IVUS, intravascular ultrasound; LDL-C, low-density-lipoprotein cholesterol; LMW, low-molecular-weight; MCP-1, monocyte chemotactic protein 1; MDA, malondialdehyde; MMF, mycophenolate mofetil; PCI, percutaneous coronary intervention; QUICKI, quantitative insulin sensitivity check index; RANTES, regulated on activation, normal T cell expressed and secreted; RAS, renin–angiotensin system; RBP-4, retinol binding protein-4; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides; VHD, valvular heart disease.

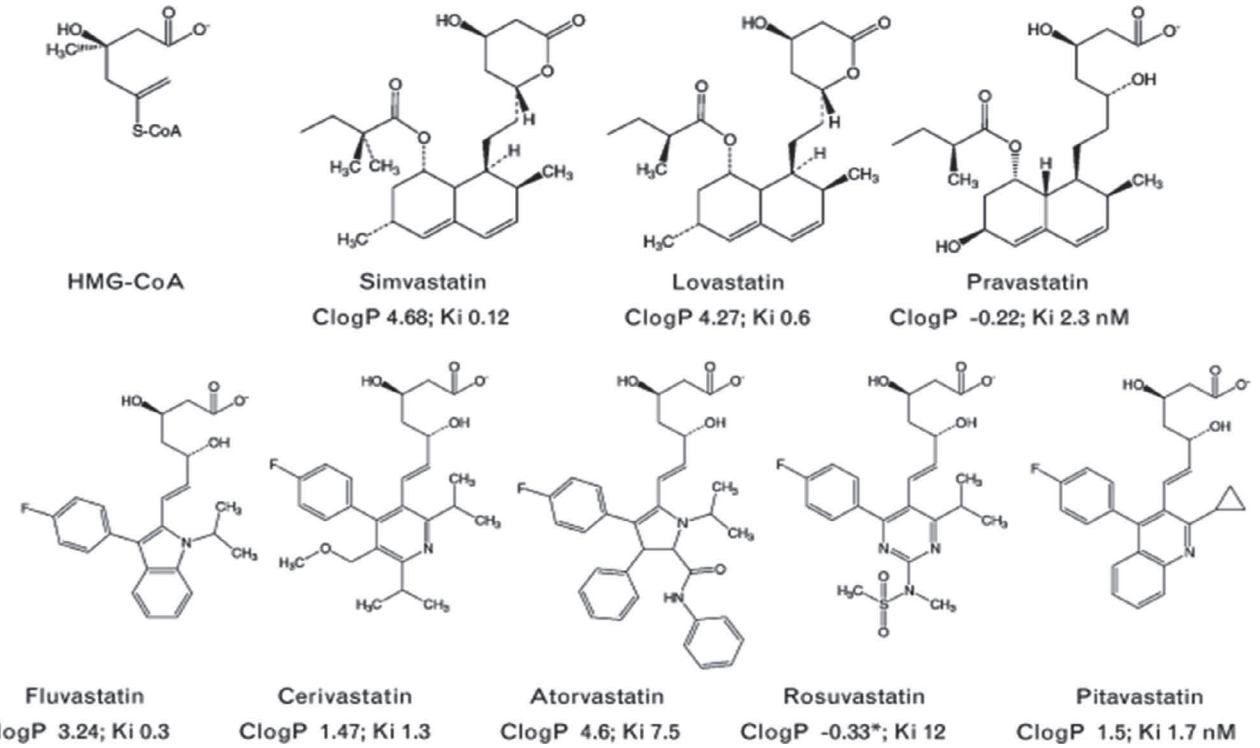

Fig. 2 Structures, lipophilicity and affinity for HMG-CoA reductase (in rat microsomes) of the most common statins. * LogD. From Arnaboldi and Corsini [72], Curr Opin Lipidol, 2010.

The specific interactions with the binding-site residues are significantly different [69]: the polar interaction mediated by the characteristic fluorophenyl group of the synthetics fluvastatin, atorvastatin, rosuvastatin and pitavastatin is lacking in the first-generation drugs lovastatin, simvastatin and pravastatin [70]. While additional hydrogen bonding characterizes atorvastatin and rosuvastatin, the peculiar cyclopropyl group confers pitavastatin avid binding and potent inhibition of HMG-CoA reductase [71] (Fig. 2). Nevertheless, statins' ability to inhibit HMG-CoA reductase

is only partially dependent on their physicochemical properties, since they are taken up by hepatocytes via active transporter system [72,73].

Moreover, statins present important pharmacokinetic differences (half-life, systemic exposure, bioavailability, protein binding, lipophilicity, metabolism, active metabolites, excretion) that contribute to their pharmacodynamic profile [68,69,72,73]. They are generally rapidly absorbed and exhibit low systemic bioavailability (5% for simvastatin, lovastatin and fluvastatin, 20% for pravastatin and rosuvastatin), except for pitavastatin (at least 51%). While all statins but pitavastatin are biotransformed by liver (thus explaining their low systemic bioavailability), intestine and liver transport proteins are also responsible for their different systemic disposition [68,69,72,73]. Lipophilic statins are extensively metabolized by cytochrome P450 (CYP) enzymes, whereas pravastatin, rosuvastatin and pitavastatin are mainly excreted unchanged [73].

Pitavastatin, thanks to its cyclopropyl group, is only slightly metabolized by CYP2C9 and CYP2C8 and is mainly excreted via biliary secretion and subjected to entero-hepatic circulation [74]. UDP-glucuronosyltransferase (UGT)-mediated lactonization of the open acid form of statins is a common pathway leading to rapid metabolism by cytochromes [73]. Atorvastatin, simvastatin, cerivastatin, rosuvastatin but not pitavastatin lactone forms undergo a 30–71- fold higher CYP3A4-mediated metabolic clearance than the open forms [75]. Indeed, in humans, the major plasma components after 2 mg-pitavastatin for 5 days are the parent compound and the lactone [74]. Altogether, the different pharmacokinetic profile of pitavastatin may lead to potentially higher systemic exposure, allowing a significant penetration into peripheral cells, thus potentially exerting extrahepatic effects, such as on adipose tissue and on adiponectin.

4.2. Pitavastatin and adiponectin: its strength in clinical studies compared to the other statins

4.2.1. *Adiponectin: role and characteristics*

Adiponectin is an antidiabetic, antiatherogenic and anti-inflammatory adipokine [76–80]. It is synthesized in adipocytes as a 32-kDa monomer, then assembled into low-molecular-weight trimers (~90 kDa), medium-molecular-weight hexamers (~180 kDa) and high-molecular-weight (HMW) multimers (12–18 monomers, > 300 kDa) [81]. Circulating adiponectin is mainly oligomeric, with physiological concentrations between 5 and 10 μg/mL (higher in women since testosterone inhibits its secretion) [82–85] and rapid plasma turnover [86].

HMW adiponectin (HMWA)'s formation and secretion are post-translationally controlled by hydroxylation [84], glycosylation and disulfide bond formation [87,88] and interconversions between oligomers do not occur after release from the adipocyte [89]. In particular, while hydroxylation and glycosylation are required for intracellular assembly of adiponectin trimers into HMW multimers [90,91], the formation of disulfide bonds between trimers or other proteins is essential for its secretion. Adiponectin succination is elevated in diabetes, suggesting that this modification may impair its secretion in obesity-related disorders.

Adiponectin exerts its effects through AdipoR1 and AdipoR2 receptors [80,92]. AdipoR1 is ubiquitous while AdipoR2 is mostly expressed in the liver [92]. Disruption of AdipoR1 blocks AMP-activated protein kinase (AMPK) activation, while disruption of AdipoR2 abolishes PPARα signalling [92]. Simultaneous disruption provokes marked glucose intolerance. The cell-surface glycoprotein T-cadherin also specifically binds HMWA [93], mediating a significant adiponectin-dependent cardioprotective effect [94].

The fact that HMWA is the most potent form [95,96] in ameliorating insulin resistance, that particularly its drops occur in parallel with deterioration of insulin sensitivity and before the appearance of diabetes [97], probably due to multimerization defects, render plasma HMWA and HMWA/total adiponectin better predictors of insulin resistance, metabolic syndrome and T2DM in humans [98–102].

Full-length adiponectin stimulates both skeletal and hepatic AMPK phosphorylation, while globular adiponectin is only active on skeletal muscle. In fact, AMPK activation is blunted in obesity and is primarily dependent on liver AdipoR1 [103,104].

While its supplementation or overexpression in transgenic mice improves insulin resistance, decreases hypertriglyceridemia and adipocyte mass, adiponectin-deficient mice are insulin resistant, glucose intolerant, dyslipidemic and hypertensive [105–107]. Epidemiological studies demonstrate a negative correlation between body fat and plasma adiponectin [108,109]. Obesity also decreases the expression of adiponectin receptors (AdipoR1 and AdipoR2) in muscle, liver and macrophages, contributing to T2DM and atherosclerosis. Significant reductions in adiponectin mRNA and concentrations in *in-vitro*, rodent models of T2DM, prospective and longitudinal trials [110–113] are associated with a higher incidence of diabetes, dyslipidemia, insulin resistance [114] and cardiovascular disease [77,112,115,116]. A recent meta-analysis [117] including 13 prospective studies with 14,598 participants and 2,623 incident cases of T2DM showed that higher plasma adiponectin is dose-dependently associated with lower T2DM risk, across diverse populations [118–121]. Finally, increases in serum adiponectin parallel weight loss, decreased plasma glucose, free fatty acids and triglycerides (TG), markedly enhancing insulin-induced suppression of glucose production, without stimulating insulin secretion [79].

In Boxes 1–7 we summarize adiponectin's properties, which are exerted on different targets and which may explain its effects on diabetes, inflammation and atherosclerosis.

Box 1. Adiponectin regulation

- Adiponectin gene transcription: upregulated by PPARα, PPARγ, SREBP-1c, C/EBP-α and FoxO1; downregulated by CREB [84].
- PPARγ:
  a. induces adipogenic gene expression during development, thus regulating lipid storage, releasing adiponectin, decreasing proinflammatory cytokines, improving liver and skeletal muscle insulin sensitivity;
  b. increases adiponectin multimerization by repriming ERp44 transcription;
  c. increases the expression of liver and skeletal muscle AdipoR1 and AdipoR2 [80,84,122].
- PPARα expressed in liver, skeletal muscle and adipose tissue, modulates fatty acid oxidation and adiponectin expression (interaction with SREBP-1c) [123].
- In response to cholesterol depletion, SREBP translocates to the nucleus, interacting also with the human adiponectin gene, promoting its transcription [124–126].
- FoxO1 is involved in adipocyte differentiation [127] and its nuclear translocation is promoted by SIRT1 [128,129].
- CREB increases hyperglycemia and insulin resistance, mainly by lowering adiponectin [79].
- TNF-α reduces mRNA expression of human adiponectin: IL-6 also mediates inflammation and CVD, by inducing hepatic CRP and liver [79].

Box 2. Adiponectin and liver

Adiponectin suppresses glucose production and output, lowering systemic glucose by:
a. enhancing hepatocyte insulin sensitivity [130,131]
b. inhibiting expression and activity of gluconeogenesis key enzymes [130,132,133]

Adiponectin's effects on hepatic insulin sensitivity are achieved by:
- ROS- or STAT-3-dependent activation of the insulin receptor,
- downstream mediators (e.g. AKT, LKB1)
- sphingolipid pathway [134,135].

Adiponectin improves liver fatty acid metabolism by:
a. decreasing circulating TG and FFA,
b. preventing hepatic steatosis in different experimental models and in humans [135–137].
   - While AdipoR1/R2 KO mice show fatty liver, overexpression of hepatic AdipoR1/R2 significantly increases hepatic ceramidase activity, therefore lowering ceramide (independently of AMPK) and improving insulin resistance [92,138].
   - AdipoR1 activation increases AMPK [92,138].
   - AdipoR2 stimulates PPARα and thus fatty-acid oxidation and energy dissipation [75,92,138].

Box 3. Adiponectin, adipose tissue, macrophages and inflammation

- Adipocytes possess immune and phagocytic properties depending on their differentiation state [78,84].
- Obesity-associated fat-mass enlargement causes adipose-tissue hypoxia [139], impaired mitochondrial function, ER stress [134] and macrophage infiltration into adipocytes, resulting in a low-grade chronic inflammation, with reduced adiponectin secretion and increased TNF-α, IL-1β, IL-6, IL-8, IL-18, TGF-β and PAI-1, as shown in rodents and obese patients [129].
- These effects are mediated by NFAT [140,141] and CREB, that during fasting stimulates liver gluconeogenic genes, enhances adipose tissue lipolysis and whose activity correlates with insulin resistance in obesity [140–145].
- Adiponectin influences adipose tissue function through AdipoR1 and AdipoR2 [146].
- Adiponectin shifts human monocyte differentiation towards macrophages with anti-inflammatory profile and prevents pro-inflammatory cytokine release, through AdipoR1 and IL-10, AdipoR2, IL-4/STAT6-dependent signaling pathway [147–151].
- Adiponectin inhibits foam-cell formation, human macrophage phagocytosis, class-A scavenger receptor expression, ACAT activity [152–156].
- In contrast, acute treatment with adiponectin releases TNF-α and IL-6, thus inducing the anti-inflammatory cytokine IL-10 [157].
- The increased expression of IL-10 and TIMP-1 in macrophages suppresses matrix metalloproteinases, enhancing plaque stability [158].
- Adiponectin-overexpressing ob/ob mice display greater subcutaneous fat (larger number of smaller adipocytes), PPARγ upregulation and improvement of adipose tissue lipid metabolism. Genes involved in fat oxidation and anti-inflammatory cytokines (IL-10) are upregulated, while inflammatory genes are suppressed [135,136,151,159,160].
- The higher TNF-α, MCP-1 and IL-6 production in adiponectin-KO mice macrophages is reduced by exogenous adiponectin [131,151,153,161].
- Adiponectin expression in adipose tissue mRNA downregulates lipogenic enzymes (FAS, ACC1, DGAT) and upregulates lipolysis [78,162].
- Ectopic adiponectin production by macrophages in transgenic mice improves systemic insulin sensitivity after high-fat diet feeding [163].
- By suppressing inflammation-induced NF-κB activation, via PPAR and AMPK and increasing IL-6 in macrophages, adiponectin activates STAT3 in hepatocytes, thereby increasing insulin sensitivity [164–166].

4.2.2. *Comparison of pitavastatin with other statins*

In-vitro and *in-vivo* studies document that statins generally reduce circulating HMWA with a concomitant increase in its intracellular concentrations, probably due to a selective secretion defect for HMWA in adipocytes [224]. Among different hypotheses, disruption of adipocyte caveolar structure, decreased adipocyte maturation/differentiation and inhibition of GLUT4 expression may represent potential mechanism(s) for statin-induced impairment of adiponectin secretion and thus of statin-induced NOD. Unfortunately, these changes do not properly translate into clinical studies,

Box 4. Adiponectin and muscle

- Probably the effects are of minor importance since globular adiponectin, the form recognized by myocyte AdipoR1, represents a very small proportion of circulating adipokine [131,167–169].
- The AdipoR1 activation upregulates AMPK, SIRT1 and PGC-1a, through AMPK phosphorylation, under sphingolipid regulation [134].
- Muscle-specific AdipoR1 disruption inhibits oxidative stress-detoxifying enzymes associated with insulin resistance, causing mitochondrial dysfunction [170].

Adiponectin causes:

Increases in:
- glucose uptake (via GLUT4 translocation),
- insulin receptor tyrosine kinase activity, p38 MAPK, non-oxidative glycolysis,
- fatty acid oxidation through PPARα activation [123].

Reductions in:
- myocellular TG [123].

In obesity models, adiponectin's effects on skeletal muscle are significantly decreased. Cultured myotubes from obese patients demonstrate impaired adiponectin-stimulated AMPK phosphorylation and fatty-acid oxidation (cellular defect in the intracellular signaling that prevents an adaptive up-regulation in the expression of AdipoR1 mRNA) [171].

Enhanced levels of NF-κB-inducing kinase (NIK), a member of the MAPK family that plays a critical role in the non-canonical NF-κB pathway, induces skeletal muscle insulin resistance *in vitro*. Adiponectin exerts its insulin-sensitizing effect by suppressing NIK-induced skeletal muscle inflammation in cultured L6 myotubes. In fact, NIK decreased in parallel with increased plasma adiponectin, enhanced skeletal muscle AMPK phosphorylation, and improved insulin sensitivity after weight loss in obese patients with the metabolic syndrome [172].

Box 5. Adiponectin and beta cells

- Effects on β-cell function are still rather speculative, with variable and inconsistent results.
- Globular adiponectin, binding to β-cells AdipoR1 [173–176], completely restores cytokine- and fatty-acid-induced impairments in glucose-stimulated insulin secretion, indicating a protective effect in β-cell dysfunction from IL-1β/interferon-γ, lipotoxicity and glucotoxicity [173–177].
- Adiponectin increases insulin secretion from isolated mouse islets by stimulating exocytosis of insulin granules, without affecting K^+/ATP channels, Ca^{2+} influx, or activation of AMPK [178].
- In insulin-resistant mouse islets (but not in normal ones), adiponectin inhibits insulin secretion at low glucose concentrations and vice versa at high concentrations [179].
- Adiponectin's antiapoptotic effects are mediated by ERK1/2, PI3K-Akt activation, but mostly by ceramidase-induced sphingosine-1-phosphate production [180–183].
- Adiponectin inhibits acetyl-CoA carboxylase activity in β-cells and glucose-stimulated lipogenesis in MIN6 cells [178,184].

Animal models:
- Adiponectin KO mice have impaired glucose tolerance but normal insulin concentrations [105].
- Globular domain adiponectin transgenic ob/ob mice exhibit increased insulin sensitivity and increased insulin secretion compared with non-transgenic mice [185].
- In C57BL/6 mice i.v. adiponectin increases insulin secretion [178].

Human studies:
- Significant associations between adiponectin and insulin levels, insulin resistance, and β-cell function are abolished after adjustment for body weight [186].
- Adiponectin correlates positively with insulin sensitivity and inversely with fasting proinsulin concentration and the proinsulin-to-insulin ratio, a marker of β-cell failure [187].
- Circulating adiponectin is correlated positively with insulin sensitivity and inversely related to β-cell dysfunction in obese subjects [188].

in which adiponectin variations and whole-body insulin sensitivity are different form statin to statin [78,225,226].

We therefore collected all the clinical studies available on PubMed up to the end of November 2014 in which the effect of simvastatin (n = 21), pravastatin (n = 14), fluvastatin (n = 1), atorvastatin (n = 36), rosuvastatin (n = 3) or pitavastatin (n = 11), alone or in head-to-head comparison, on plasma total adiponectin was measured. We could not find any published trial documenting the effect of lovastatin on adiponectin. Tables 2–6 thoroughly summarize these trials, highlighting:
- type of population,
- number of patients enrolled,
- statin dose, alone or coadministered with other drugs, and duration of treatment,
- basal concentrations of plasma adiponectin (where available) and % changes vs baseline,
- other outcomes (lipid and glucose profiles, markers of atherosclerosis and diabetes).

We depict in Fig. 3 the effect of treatment with different statins on the percent change in total plasma adiponectin. Pitavastatin clearly emerges as the best statin on this parameter, increasing adiponectin concentrations by 27.2±15.9%. Rosuvastatin and pravastatin are less effective, enhancing adiponectin by 17.3±37.2% and 14.7%±32.5%, respectively. On the other hand, atorvastatin and fluvastatin (data not shown, since only one study is available) are uneffective (+7.2±20.5% and 0%, respectively), while simvastatin even decreases adiponectin concentrations (−1.6±17.5%). The elevated SD in the results obtained with simvastatin (in

Box 6. Adiponectin and HDL

- Plasma and HMW adiponectin directly correlates with HDL-C in healthy subjects and diabetics, while it inversely correlates with apoA1 catabolism, independently of obesity and insulin resistance.
- *In-vitro* and *in-vivo* studies suggest causality and bidirectionality in adiponectin–HDL relationship [189–195].
- Direct role for adiponectin in HDL catabolism [196].
- In a prospective trial conducted in obese women, physical activity plus mediterranean diet reduced body weight, increased adiponectin and HDL, and decreased insulin resistance, serum FFA, IL-6 and IL-18 [162].
- Plasma adiponectin is lowered in CHD patients [116,159,162,197].
- HDL-C represents an important connection between adiponectin and CHD risk. Increased ceramidase activity, adipose tissue IL-6, CRP, PAI-1 and TNF-α mediate this effect [134].
- Adiponectin increases HDL-C via
  a. enhancing ApoA-I and ABCA1 production (through PPARγ), thus inducing RCT in rodents but also in humans [198–203].
  b. increasing mitochondrial fatty-acid oxidation, reducing circulating FFA, thus reactivating LPL and downregulating HL or activating PPARα, that upregulates liver apoAI/AII expression, increasing reverse cholesterol transport [204].
- HDL mobilize adipocyte unesterified cholesterol, while apoA-I overexpression reduces adipose tissue mass of high-fat fed mice [205], by enhanced energy expenditure and stimulation of AMPK.
- Adiponectin may mediate the insulin-sensitizing effects of HDL by activation of AMPK in skeletal muscle [206].

Box 7. Sirtuin, type 2 diabetes mellitus and adiponectin

Sirtuin-1 (SIRT1), a class-III histone deacetylase, delays aging and age-related diseases of glucose-lipid metabolism [207] through:
- regulation of insulin secretion [208],
- protection of pancreatic β-cells [209],
- improvement of insulin resistance via modulation of post-insulin receptor signaling [210],
- decrease of inflammation, lipid mobilization and regulation of hepatic glucose production via FoxO1 and PPARγ [210].
- Enhancement of fasting-induced mitochondrial fatty acid oxidation by activating liver PPARα and PGC-1α, inhibiting SREBP-1C activity and increasing LXR [211–213].
- Protection against oxidative-stress-induced insulin resistance, by restoring mitochondrial oxidative capacity, increasing antioxidant enzymes and FOXO3a [214,215].
- Induction of hepatic gluconeogenesis (by PGC-1α and FOXO1) in late fasting conditions [216].
- *Sirt1* transgenic mice present increased lipolysis and adiponectin levels, reduced blood cholesterol, insulin, fasting glucose and good glucose tolerance [217–220].
- SIRT1-KO mice exhibit reduced body weight, smaller-sized adipocytes, reduced adiponectin, leptin and adipocyte differentiation [221].
- Decreased SIRT1 expression is present in insulin resistance and glucose intolerance, due to physical interaction with the NF-κB p65 subunit [222,223].

10 of 23 studies the drug decreased adiponectin, in 11 it did not cause a significant change and only in 2 it increased adiponectin), atorvastatin (12 decreases, 15 no change and 15 increases) but mostly with rosuvastatin (2 decreases, 5 no change and 4 increases) and pravastatin (4 decreases, 1 no change, 9 increases) reflect the discrepancies in results and the different magnitudes of the effect. Interestingly, pitavastatin is the only statin that consistently and significantly increases adiponectin (9/10 positive and 1/10 ineffective trial), without negative outcomes on this parameter, both when used alone and in head-to-head trials with other statins. These results may suggest a link between pitavastatin and the findings on its neutral–beneficial effect on glucose metabolism.

In order to understand whether specific populations can benefit more from a statin-induced plasma adiponectin increase, we divided the results of the trials into three tertiles, performing a kind of "basal adiponectin-based selection". As suggested from literature, subjects with values lower than 5 μg/mL are considered hypoadiponectinemic, while those with values between 5 and 10 μg/mL are normoadiponectinemic [227]. Values higher than 10 represent hyperadiponectinemic subjects. The results of this analysis are depicted in Fig. 4. Except rosuvastatin, though with different efficacy, all the other statins seem to be most effective in increasing adiponectin in hypoadiponectinemic patients, with pitavastatin being the most promising.

5. Conclusions

In-vitro, *in-vivo*, but mainly clinical studies demonstrate that pitavastatin, unlike most of the available statins, does not worsen or even ameliorates glucose metabolism markers, but the mechanism is still unknown. Keeping in mind the possibility that statins' diabetogenicity could be due, at least in part, to an on-target reduction of HMG-CoA reductase activity [17], beyond pharmacokinetic differences (striking higher oral bioavailability, lower hepatic extraction and higher systemic exposure compared with the other statins), constant and significant increases of plasma total adiponectin characterize pitavastatin's effect. Adiponectin is an anti-inflammatory, antiatherosclerotic and antidiabetic protein, whose concentrations are reduced in T2DM, hyperlipidemia and metabolic syndrome. Since its positive effects are exerted on adipose tissue, liver, HDL metabolism and pancreatic beta cells, the peculiar property of pitavastatin

Table 2
Effect of atorvastatin on adiponectin in clinical studies

First author [ref.]	Patients	Drug, duration and dose	Effect on adiponectin	Other effects
Son [228]	440 T2DM patients.	8-week, titration trial of tailored atorvastatin (10, 20, 40 mg/day), according to baseline LDL-C.	Adiponectin increased: from 6.58 to 7.22 (+9.7%), from 7.53 to 8.2 (+8.9%), from 7 to 7.42 (+6%) for 10, 20 and 40 mg atorvastatin respectively.	Tailored atorvastatin ameliorated LDL size, inflammation and achieved the target LDL-C without affecting glycemic control.
Al-Azzam [229]	394 T2DM patients.	161 patients treated with 20 mg/day atorvastatin vs 233 controls.	Atorvastatin treatment is not associated with changes in adiponectin (basal 2.1 μg/mL).	No changes in leptin, leptin/adiponectin or HOMA-IR. Significant positive correlation HDL-C/adiponectin in both groups.
Tanaka [230]	29 T2DM patients (16 males).	Single pill of amlodipine 5 mg/ atorvastatin 10 mg for 6–12 months	Adiponectin increased (6.7%) only after 12 months (from 7.64 to 8.15 μg/mL).	LDL-C, TG, mean IMT, urinary albumin/creatinine ratio and creatinine significantly decreased at 6 and 12 months. eGFR increased.
Buldak [231]	67 patients with impaired fasting glucose and mixed dyslipidemia.	Atorvastatin, fenofibrate, their combination, or therapeutic lifestyle change for 90 days.	Drug therapies increased adiponectin and decreased leptin and resistin.	Significant alterations in the lipid profile. Fenofibrate reduced HOMA-IR. Additive effect on plasma IL-6 by the combination.
Hyogo [232]	42 NASH patients with dyslipidemia.	atorvastatin (10 mg/day) for 12 months.	Atorvastatin increased adiponectin by 16.4% (from 5.5 to 6.4 μg/mL).	Atorvastatin increased HDL-C, improved NASH, significantly decreased liver transaminase, γ-GGT, LDL-C, TG and TNF-α.
Szotowska [233]	36 patients with metabolic syndrome and LDL-C > 3.5 mmol/l, previously untreated with statins.	2, 4 and 6 months of atorvastatin therapy (10 mg).	Plasma adiponectin significantly decreased by 20.7% after 2 months vs baseline (8.54 μg/mL); the decrease lost significance at 4 and 6 months vs baseline.	−35.6% LDL-C.
Li [234]	25 patients with CAD, HC hypertension.	Combination amlodipine–atorvastatin in 8 dosages for 14 weeks.	The combination increases adiponectin (49.4%; 12.1 vs 8.1 μg/mL); the increase correlated with FMD and changes in diastolic blood pressure.	Reduced systolic and diastolic blood pressure, TC and LDL-C.
El-Barbary [235]	30 patients with early rheumatoid arthritis plus 10 healthy controls.	(A) 15 treated for 6 months with methotrexate 0.2 mg/kg/week plus prednisone 10 mg /day. (B) 15 additionally received atorvastatin 40 mg/day.	Adiponectin significantly improved by the treatments: Group A from 19.81 to 21.61 (9%) and Group B from 19.21 to 23.36 μg/mL (21.6%), respectively.	Atorvastatin/metotrexate significantly reduced TC, LDL-C and TG, and increased HDL-C. TNF-α, FMD and resistin significantly improved.
Carnevale [236]	36 patients with polygenic HC plus 18 healthy controls.	Low-fat diet (Group A) or low-fat diet plus atorvastatin 10 mg/day (Group B) for 30 days	Adiponectin significantly increased in group B (83.6%; from 5.5 to 10.1 μg/mL), which inversely correlated to reduced levels of urinary isoprostanes, platelet oxygen free radicals.	Patients presented lower serum adiponectin, worse lipid profile, urinary isoprostanes, platelet oxygen free radicals.
Koh [237]	213 HC patients.	44 patients treated with placebo; 42, 44, 43 and 40 patients treated with atorvastatin 10, 20, 40, 80 mg/day, respectively, for 2 months	Atorvastatin 10, 20, 40 and 80 mg decreased plasma adiponectin (−4%, −10%, −3%, and −9%, respectively) after 2 months. Compared vs placebo these effects were not significant.	Atorvastatin significantly reduced LDL-C and apo B vs baseline or placebo, increased fasting plasma insulin and HbA1c, and decreased insulin sensitivity.
Satoh [238]	25 patients without CAD and 70 patients with stable CAD not previously treated with RAS blockers or statins.	Patients without CAD received no treatment. CAD patients received either telmisartan 40 mg/day or enalapril 5 mg/day (1:1 ratio) for 6 months and both groups received atorvastatin 10 mg/day.	Telmisartan significantly increased HMW- and HMW/total adiponectin ratio; After telmisartan or enalapril, HMWA was 0.7 μg/mL in CAD vs 3.2 in controls; HMW/total adiponectin was 0.25 in CAD vs 0.43 in controls.	Telmisartan and enalapril decreased hs-CRP. HOMA-IR significantly decreased vs baseline. Basal HMW- and HMW/total adiponectin were lower in CAD vs controls (2.0 vs 9.2 μg/mL and 0.37 vs 0.53). Baseline HMW adiponectin negatively correlated with hs-CRP and HOMA-IR in CAD.
Nakamura [239]	47 HC patients with stable CAD.	Atorvastatin 10 mg/day (n = 16), bezafibrate 400 mg/day (n = 15) or placebo (n = 15) for 1 and 6 months	Atorvastatin increased adiponectin from 2.05 to 2.72 (+32%) and 3.24 (+58%) μg/mL at 1 and 6 months vs baseline respectively. Similar increases with bezafibrate.	Significant correlation between adiponectin and FMD; inverse correlation between adiponectin, HOMA-IR, TNF-α CRP and TG. Atorvastatin and bezafibrate similarly increased FMD and decreased HOMA-IR, CRP and TNF-α.
Koh [225]	42 patients with hypertension.	(a) Atorvastatin 20 mg/day and placebo; (b) atorvastatin 20 mg/day and amlodipine 10 mg/day; (c) amlodipine 10 mg/day and placebo for 2 months followed by a 2-month washout period.	Atorvastatin significantly decreased [from 3.3 to 3 μg/mL (−10%)] and amlodipine increased [from 3.2 to 3.6 μg/mL (+12.5%)] plasma adiponectin. Their combination significantly increased adiponectin [from 3.2 to 3.9 μg/mL (+21.9%)] and insulin sensitivity relative to baseline.	Amlodipine alone or in combination significantly reduced blood pressure. Atorvastatin/amlodipine improved FMD significantly more than the single drugs. Atorvastatin increased, while amlodipine decreased insulin levels.
Arca [240]	48 FCHL patients.	Atorvastatin 10 mg/day (n = 22) or fenofibrate (n = 26) for 24 weeks	Adiponectin was increased by 12.5% (from 8.19 to 9.36 μg/mL) by atorvastatin and reduced by 10% by fenofibrate.	FCHL patients and normolipidemic relatives had lower serum adiponectin vs controls.
van Hoek [241]	194 patients with T2DM and mildly elevated TG.	6 months of placebo, 10 or 80 mg/day atorvastatin.	Atorvastatin had no effect on plasma adiponectin. Patients with the highest basal adiponectin displayed the largest increase in HDL-C.	At baseline, plasma adiponectin levels were associated positively with HDL-C and negatively with TG.

continued on next page

Table 2
(*continued*)

First author [ref.]	Patients	Drug, duration and dose	Effect on adiponectin	Other effects
Hyogo [242]	31 patients with biopsy-proven NASH with hyperlipidemia.	atorvastatin 10 mg/day for 24 months.	Adiponectin levels significantly increased (24.5%) from 5.3 to 6.6 μg/mL.	TNF-α and long-chain fatty acids significantly decreased, while leptin did not change. Liver steatosis significantly improved, but 4 patients had fibrosis.
Forst [243]	148 patients with increased CV risk factors (76 male, 72 female; age 61.4±6.5 years; BMI 29.2±4.1 kg/m^2).	atorvastatin 20–40 mg/day monotherapy or combined with pioglitazone for 6 months.	No effect of atorvastatin (from 14.8 to 14.3 μg/mL). Addition of pioglitazone to atorvastatin significantly increased adiponectin from 15.7 to 32.0 μg/mL (103.8%).	Atorvastatin alone and in combination with pioglitazone caused a significant regression in IMT. Addition of pioglitazone significantly ameliorated t-PA, TG, hs-CRP, P-selectin and HDL-C.
Teplan [244]	68 obese renal transplanted patients (BMI > 30 kg/m^2) with dyslipidemia.	Tailored diet up to one year after transplantation, followed by corticosteroid withdrawal and atorvastatin 10–20 mg/day, plus cyclosporin A or MMF/tacrolimus.	Significant increase in adiponectin due to corticosteroid withdrawal and switch to statin, cyclosporin A or MMF/tacrolimus and long-term diet.	Significant decrease in BMI, serum leptin and lipid metabolism markers.
von Eynatten [245]	75 patients with T2DM (23 females; 52 males).	Atorvastatin 40 mg/day for 8 weeks vs placebo.	HMW adiponectin significantly increased (42.3%, 1.68 vs. 2.39 μg/mLl); MMW and LMW adiponectin significantly decreased (MMW: 20.8%, from 3.31 to 2.62 μg/mL; LMW: 23.2%, from 0.56 to 0.43 μg/mL). Total adiponectin was not significantly altered (6.0 vs. 6.2 μg/mL). HMW/total adiponectin significantly increased by 25.0%.	–
Chan [246]	60 coronary artery disease patients with stable angina and normal lipid profiles scheduled for PCI and not on statins.	No treatment or atorvastatin immediately after PCI for 3–6 months.	Significant decreases in adiponectin after 3 and 6 months of atorvastatin [from 8.66 to 6.87 μg/mL (−21%) and 7.12 μg/mL (−18%) at 3 and 6 months, respectively], but not in controls.	Significant positive association baseline plasma adiponectin/HDL. Changes in adiponectin not associated with those of hs-CRP and of lipids.
Blanco-Colio [247]	102 statin-free Spanish subjects with CHD, CHD-equivalent or a 10-year CHD risk > 20% vs 40 age- and gender-matched blood donors.	Atorvastatin 10–80 mg/day based on LDL-C at screening.	In whole population, atorvastatin dose-dependently increased adiponectin levels (9.7%). The dose-dependent increase ranged from 2.2% to 24.7% with atorvastatin 10–80 mg/day	Adiponectin levels were reduced in patients at high CHD vs controls. Adiponectin positively correlated with HDL-C before and after atorvastatin.
Chu [248]	29 HC, T2DM patients (15 males, 14 females).	Atorvastatin 10 mg (n = 10), 20 mg (n = 10) or 40 mg (n = 9) for 12 weeks	No difference in adiponectin levels.	No differences in insulin, leptin, HOMA and QUICKI before and after treatment. TC, LDL-C and TG significantly decreased.
Miyagishima [249]	22 patients with ischemic heart disease and LDL-C > 100 mg/dl.	Atorvastatin 10 mg/day for 3 months	Adiponectin significantly increased (43.3%) from 9.7 to 13.9 μg/mL.	Atorvastatin significantly decreased serum lipids, ox-LDL.
Otto [250]	13 patients with T2DM and mixed hyper-lipoproteinemia (5 males, 8 females, age 60.0±6.8 years, BMI 30.0±3.0 kg/m^2).	Atorvastatin 10 mg/day and fenofibrate 200 mg/day each for 6 weeks separated by a 6-week washout.	No changes in adiponectin.	No changes in ghrelin, resistin and insulin levels
Chu [251]	32 HC patients.	Atorvastatin 10 mg/day for 3 months.	No significant changes in adiponectin levels.	sCD40L, TC and LDL-C significantly reduced.
Bayes [252]	Kidney transplant recipients with stable renal function and dyslipidemia (41 males, 27 females; mean age 53 years).	Atorvastatin 10 mg/day for 12 weeks	No changes in adiponectin levels. Inverse correlation adiponectin/glucose, insulin, HOMA-IR index and positive correlation adiponectin/HDL-C.	Atorvastatin significantly ameliorated lipid profile but did not modify glucose homeostasis, TNF-α or CRP.
Koh [253]	56 patients with combined hyperlipidemia.	Atorvastatin 10 mg/day, fenofibrate 200 mg/day, or their association, for 2 months.	Adiponectin increased with fenofibrate alone or in combination (from 3.2 to 3.6 and 3.4 to 3.5 μg/mL respectively), while atorvastatin alone did not (from 3.5 to 3.4 μg/mL).	The combination was significantly better than the single drugs on lipoprotein profile, FMD, hs-CRP and fibrinogen levels.
Shetty [192]	77 subjects who had diabetes or were at high risk of developing diabetes.	Atorvastatin 20 mg/day for 12 weeks.	Atorvastatin did not alter resistin and adiponectin. Positive correlation adiponectin/HDL and CRP; negative with BMI, TG, CRP and PAI-1.	Atorvastatin decreased lipid and CRP levels.

See Table 1 for abbreviations.

in increasing adiponectin may explain, at least in part, its neutral or even beneficial effects on glucose metabolism and on NOD incidence (Fig. 5).

Nevertheless, we cannot exclude that other mechanism(s) may contribute to these properties [301–310]. Among these, an effect on HDL metabolism (Box 8) may be involved, since, as demonstrated in Table 7, pitavastatin constantly increases their concentrations in several clinical studies. Further studies are required to confirm the real beneficial effect of pitavastatin administration on the risk of NOD.

Table 3
Effect of simvastatin on adiponectin in clinical studies

First author [ref.]	Patients	Drug, duration and dose	Effect on adiponectin	Other effects
Krysiak [254]	42 adult patients with untreated isolated HC vs 18 normolipidemic controls.	1 month of lifestyle intervention alone (n = 19) or plus 40 mg/day simvastatin (n = 23) vs 18 healthy subjects.	Simvastatin increased plasma adiponectin [from 5.2 to 6.8 mg/l (30.7%)] vs untreated (from 5.7 to 5.5) and healthy subjects (10.7 to 11.2).	Simvastatin reduced plasma free fatty acids, leptin and TNF-α. No differences in plasma adipokines between insulin-resistant and insulin-sensitive subjects.
Lazich [255]	53 patients with metabolic syndrome.	Simvastatin 40 mg/day alone or plus rosiglitazone 4 mg/day for 6 months.	Adiponectin increased only when simvastatin was associated with rosiglitazone.	Simvastatin/rosiglitazone reduced CRP and decreased blood glucose vs placebo.
Hu [256]	57 patients: 23 T2DM and atherosclerotic, statin-treated; 20 T2DM atherosclerotic and 14 T2DM non-atherosclerotic statin-untreated for the last 3 months.	Simvastatin 40 mg/day for 12 weeks.	Adiponectin increased by 59.6% vs baseline.	LDL-C decreased and HDL-C increased. CRP, TNF-α and IL-6 decreased.
Kater [257]	50 prediabetic subjects with normo- or mild-to-moderate HC	Ezetimibe 10 mg/day or simvastatin 20 mg/day for 12 weeks, after which the drugs were combined for another 12 weeks.	No changes in HOMA and adiponectin.	Single drugs significantly reduced TC- and LDL-C, apoB and TG. Additional reductions when combined (E-selectin, ICAM-1). PAI-1 and urinary albumin excretion were lowered by simvastatin.
Pfutzner [258]	125 nondiabetic patients at high CV risk (78 females, 47 males, age 58.6 years; BMI 30.8 kg/m^2)	Pioglitazone 45 mg, simvastatin 40 mg or combination for 3 months.	Pioglitazone alone or combined significantly improved HOMA-IR and adiponectin. Simvastatin decreases adiponectin.	Reductions of CRP with all the treatments. No changes in plasma RBP4.
Koh [259]	89 HC and/or T2DM patients.	45 patients treated with simvastatin 20–40 mg/day vs 44 controls for 2 months.	Simvastatin 20 and 40 mg/day significantly decreased adiponectin [from 5.7 to 5.2 μg/mL (−8.9%) and from 6.8 to 6.1 μg/mL; (−10.3%), respectively] and insulin sensitivity.	Simvastatin 20–40 mg significantly increased plasma leptin, while simvastatin 40 mg decreased plasma resistin.
Hajer [260]	15 nonsmoking, male, obese patients with metabolic syndrome.	Simvastatin 80 mg vs simvastatin/ezetimibe 10 mg/10 mg for 6 weeks on post-prandial HDL-C.	8 hours after fat loading adiponectin decreased with both treatments (−8.4% and −6.4%, respectively).	Stable HDL-C during continuous fasting following an overnight fast. Fat load induced an 11% drop in HDL-C, unaffected by either therapy.
Koh [261]	156 HC patients.	32 patients received placebo; 30, 32, 31, 31 patients received 10, 20, 40, 80 mg/day simvastatin for 2 months.	Simvastatin 10, 20, 40 and 80 mg significantly and equally decreased adiponectin [6.4 to 5.9 μg/mL (−8%), 6 to 5.3 μg/mL (−10.7%), 6.2 to 5.7 μg/mL (−8.1%) and 6.4 to 5.7 μg/mL μg/mL (−10.3%), respectively].	Simvastatin 10–80 mg significantly reduced insulin sensitivity, TC, LDL-C and apo B, and improved FMD.
Gouni-Berthold [262]	72 healthy males (mean age 32 years, BMI 25.7 kg/m^2).	Each group of 24 subjects received either ezetimibe 10 mg/day, simvastatin 40 mg/day, or their combination, for 14 days.	Neither ezetimibe nor simvastatin or their combination had any effect on serum leptin, adiponectin, HMWA or resistin.	Baseline leptin levels correlated positively, while adiponectin and HMW adiponectin correlated negatively with BMI. Adiponectin and HMW adiponectin correlated with HDL-C.
Pfutzner [263]	125 nondiabetic patients at CV risk (78 females, 47 males, mean age 58.6 years; BMI 30.8 kg/m^2).	Pioglitazone 45 mg, simvastatin 40 mg, or their association, for 3 months.	Increase in adiponectin with pioglitazone groups, but decrease with simvastatin alone [from 15.5 to 11.6 μg/mL (−25.1%)].	Improvement in the HOMA-IR score with pioglitazone groups. No changes in visfatin.
Devaraj [264]	50 patients with metabolic syndrome.	Simvastatin 40 mg/day vs placebo for 8 weeks.	Simvastatin did not affect circulating adiponectin levels vs placebo.	Simvastatin did not affect insulin sensitivity.
Forst [265]	105 nondiabetic patients at CV risk.	Pioglitazone 30–45 mg/day in comparison with, and in combination with, simvastatin 20–40 mg.	Adiponectin increased with pioglitazone alone or in combination [from 13.96 to 27.64 μg/mL (+98%) and from 11.68 to 26.67 μg/mL (+118.3%), respectively], while it decreased with simvastatin [from 15.5 to 11.6 μg/mL (−25.1%)].	Lipid profile improved with simvastatin. The combination was superior to the single drugs in improving overall CV risk profile.
Bulcão [266]	41 subjects with BMI > 25 kg/m^2 and impaired fasting glucose or impaired glucose tolerance.	Simvastatin 20 mg/day (n = 20) or metformin 1.7 g/day (n = 21) for 16 weeks.	No change in leptin or adiponectin by any therapy.	Metformin significantly reduced mean BMI, insulin resistance and waist circumference. Simvastatin significantly reduced LDL and TG. Both decreased CRP.
Koh [267]	50 T2DM patients.	Simvastatin 20 mg/day, ramipril 10 mg/day, or their association for each 2-month period.	Ramipril, alone or in combination, but not simvastatin, significantly increased plasma adiponectin and insulin sensitivity.	Ramipril alone or in combination reduced blood pressure vs simvastatin. Simvastatin alone or in combination significantly improved lipid profile. All regimens significantly improved FMD and reduced MDA.
Koh [268]	47 hypertensive, HC patients	Simvastatin 20 mg/day, losartan 100 mg/day, or their association, each for 2 months.	Losartan alone or in combination significantly increased adiponectin and insulin sensitivity.	Losartan alone or in combination significantly reduced blood pressure vs simvastatin. Simvastatin alone or in combination significantly improved lipid profile. The regimens significantly improved FMD, and decreased MDA and MCP-1.

See Table 1 for abbreviations.

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Table 4
Effect of fluvastatin, pravastatin and rosuvastatin on adiponectin in clinical studies

First author [ref.]	Patients	Drug, duration and dose	Effect on adiponectin	Other effects
Sonmez [269]	49 dyslipidemic patients (27 males, 22 females; mean age 47.2 years; BMI 29.6 kg/m^2) and 20 controls (6 males, 14 females; mean age 45.3 years; BMI 30 kg/m^2).	Initial therapeutic lifestyle changes for 6 weeks. 24 HC patients also received fluvastatin 80 mg/day for 12 weeks.	Therapeutic lifestyle changes significantly improved plasma insulin and increased plasma adiponectin [6.4 to 8.2 μg/mL (28.1%)]. No effect of fluvastatin on plasma insulin, adiponectin or HOMA index.	Fluvastatin significantly decreased TC and LDL-C.
Takagi [270]	152 blood samples from WOSCOPS biobank.	78 pravastatin-treated vs 74 controls (1 year).	Pravastatin significantly increased plasma adiponectin (controls −0.28; pravastatin +1.47 μg/mL vs baseline).	–
Ruscica [271]	30 moderately dyslipidemic patients with metabolic syndrome.	Pravastatin 10 mg/day for 8 weeks.	Adiponectin decreased from 6.3 to 5.6 μg/mL (−11.2%).	Decreases in TC and LDL-C.
Koh [272]	48 HC patients (23 with metabolic syndrome).	Pravastatin 40 mg, valsartan 160 mg/day, or their association, each for 2 months.	All treatments increased plasma adiponectin [pravastatin: from 2.97 to 3.38 μg/mL (13.8%); association: from 2.81 to 3.73 μg/mL (32.7%)].	FMD and CRP greatly improved with combined therapy. All treatments reduced fasting insulin and increased insulin sensitivity.
Kim [273]	73 HC females with T2DM.	Placebo vs pravastatin 20 or 40 mg/day for 16 weeks.	No significant differences between baseline and pravastatin 20–40 mg/day on total adiponectin (from 3.22 to 2.88 and from 3.19 to 3.3 μg/mL, respectively), and on total/HMW adiponectin, or insulin sensitivity.	TC and LDL-C significantly reduced after pravastatin 20 and 40 mg vs placebo.
Fichtenbaum [274]	74 dyslipidemic patients (37 per arm).	Pravastatin 40 mg/day or fenofibrate 200 mg/day for 12 weeks. 60 patients who failed mono-therapy received the combination, weeks 12–48.	At week 48 adiponectin decreased with pravastatin [from 4.5 to 4 μg/mL (−11.1%)], but not with fenofibrate.	No significant changes in CRP, PAI-1, and P-selectin. From baseline to week 12, Apo B decreased for both arms and also after 48 weeks. Apo A1 increased.
Nezu [275]	94 Japanese dyslipidemic patients without previous CAD.	Pravastatin 10 mg/day for 6 months.	Total adiponectin concentration significantly increased [from 11.7 to 13.7 μg/mL (17%)].	Concomitant thiazolidinedione synergistically influenced the effect.
Kai [276]	26 mild HC and hypertensive patients.	Pravastatin 10 mg/day for 6 months, then 20 mg/day.	Total- and HMW adiponectin significantly increased moving to 20 mg/day [from 10.9 to 12.6 μg/mL (15.6%) and from 6.6 to 7.6 μg/mL (15.2%), respectively].	Increasing pravastatin from 10 to 20 mg/day decreased LDL-C.
Sugiyama [277]	40 CAD patients with IGT.	Pravastatin (n = 20) or no lipid-lowering drugs (control, n = 20) for 6 months.	Pravastatin significantly elevated plasma adiponectin from 5.2 to 6.1 μg/mL (17.3%).	Pravastatin significantly decreased TC, LDL-C and CRP, and improved hyperglycemia and hyperinsulinemia.
Sakamoto [278]	115 HC patients (83 males, 32 females; mean age 68 years) with documented CAD. Patients were divided into quartiles Q1 to Q4 according to increased basal serum adiponectin.	Pravastatin 10–20 mg/day for 6 months.	Serum adiponectin significantly increased in 74 patients (64.3%) [from 7.2 baseline to 7.8 μg/mL (8.3%)]. The increase was significantly higher in patients in Q1 (39.3%) compared with those in Q3 (4.5%) and Q4 (6.3%).	Pravastatin decreased TC, LDL-C and CRP, and increased HDL-C. Adiponectin increase significantly correlated with that in HDL-C.
Gannagé-Yared [279]	40 healthy nondiabetic subjects (22 males, 18 females; age 28–72 years).	Pravastatin 40 mg/day vs placebo for 12 weeks.	Pravastatin did not alter adiponectin and leptin levels. Negative correlation of adiponectin with BMI and positive with HDL-C.	Pravastatin decreased TC, LDL-C and TG, but did not affect glucose and insulin levels.
Kim [280]	53 patients with mild to moderate hypertension.	Rosuvastatin 20 mg/day (n = 27) vs controls (n = 26) for 8 weeks (on top of anti-hypertensive drugs).	Plasma adiponectin did not differ significantly from controls.	Rosuvastatin improved TC, LDL-C and TG, without changes in fasting glucose levels and insulin resistance.
Doh [281]	70 patients undergoing peritoneal dialysis.	Rosuvastatin 10 mg/day (n = 35) vs placebo (n = 35) for 6 months.	Rosuvastatin did not improve adipokine profiles.	Rosuvastatin significantly decreased HOMA-IR and CRP vs baseline.
Tasci [282]	116 patients with isolated dyslipidemia.	Therapeutic lifestyle change for 12 weeks. In 54 patients, LDL-C decreased < 160 mg/dL. The remaining 62 non-responding patients were treated with rosuvastatin 10 mg/day for 12 weeks.	Both LDL-C-lowering regimens increased adiponectin. In those not responding to therapeutic lifestyle change, rosuvastatin increased adiponectin from 5.5 to 11.57 μg/mL (110%).	No significant change in plasma apelin in non-respondents to therapeutic lifestyle changes. LDL-C lowering increased plasma apelin. Lifestyle changes, but not rosuvastatin decreased serum leptin. TNF-α and plasma CRP decreased with rosuvastatin.

See Table 1 for abbreviations.

Table 5
Effect of pitavastatin on adiponectin in clinical studies

First author [ref.]	Patients	Drug, duration and dose	Effect on adiponectin	Other effects
Arao [45]	16 patients with stable CAD and mild dyslipidemia, and 6 age-matched healthy controls.	Pitavastatin 2 mg/day for 6 months.	In CAD patients, pitavastatin increased plasma adiponectin from 6.19 to 7.45 μg/mL (20.4%)	Pitavastatin significantly improved lipid profile.
Nomura [41]	191 hyperlipidemic patients with T2DM vs 30 normolipidemic controls.	Pitavastatin 2 mg/day (n = 64), EPA 1,800 mg/day (n = 55), or their combination (n = 72), for 6 months.	Pitavastatin, alone and in association, but not EPA, significantly increased adiponectin [from 3.29 to 4.16 μg/mL (26.4%) and from 3.24 to 4.02 μg/mL (24.1%), respectively].	Basal adiponectin in patients was lower than in controls.
Ohbayashi [283]	42 HC outpatients (21 males, 21 females; mean age 65.2 years).	Pitavastatin 2 mg/day for 12 weeks.	Serum resistin, but not adiponectin and leptin, significantly decreased.	Pitavastatin significantly decreased LDL-C.
Inami [284]	117 patients with hyperlipidemia.	Pitavastatin 2 mg/day for 6 months.	Pitavastatin significantly increased adiponectin in hyperlipidemic patients with or without T2DM [from 3.52 to 4.52 μg/mL (28.4%) and from 3.48 to 4.23 μg/mL (21.6%), respectively].	In T2DM patients basal adiponectin was lower than in controls. Pitavastatin significantly decreased TC and LDL-C. No differences in CRP, platelet-derived microparticles and sP-selectin.
Nomura [285]	75 hyperlipidemic patients with and without T2DM vs 35 normolipidemic controls.	Pitavastatin 2 mg/day for 6 months.	Pitavastatin significantly increased adiponectin in hyperlipidemic T2DM patients [baseline vs 3 and vs 6 months: 2.81 vs 3.84 μg/mL (36.7%) and vs 4.61 μg/mL (64.1%)]. Adiponectin was lower in hyperlipidemic patients vs controls.	Significant correlation adiponectin/sE- and sL-selectin in T2DM patients. Pitavastatin significantly decreased TC and LDL-C. sE- and sL-selectin decreased in hyperlipidemic diabetics. No differences in MCP-1, RANTES and sCD40L.
Matsubara [286]	94 HC patients, with (62) or without (32) metabolic syndrome.	Pitavastatin 2 mg/day for 12 weeks.	In patients with metabolic syndrome, HMW-adiponectin did not change. When divided in two subgroups according to % change in HDL-C, a significant increase in HMW-adiponectin (18%) was observed in the HDL-C ⩾10% increase subgroup vs the HDL-C < 10% increase subgroup (−4%).	In patients with metabolic syndrome, plasma hs-CRP was significantly higher and HMW-adiponectin significantly lower than in those without. Baseline HMW-adiponectin and HDL-C significantly correlated in patients with metabolic syndrome.
Nomura [287]	68 hyperlipidemic patients vs normolipidemic controls	Pitavastatin 2 mg/day for 6 months.	Pitavastatin significantly increased adiponectin from 3.49 to 4.36 μg/mL (24.9%). Significant decreases in plasma PAI-1 and sCD40L after pitavastatin in adiponectin responders.	Hyperlipidemic patients had higher plasma CD40L, sP-selectin and PAI-1 and lower adiponectin. No significant differences in plasma sCD40L, sP-selectin and PAI-1 before and after treatment.

See Table 1 for abbreviations.

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Table 6
Effect of different statin regimens on adiponectin in clinical studies

First author [ref.]	Patients	Drug, duration and dose	Effect on adiponectin	Other effects
Toyama [288]	28 CAD patients.	Rosuvastatin (n = 14) or atorvastatin (n = 14) combined with regular exercise, for 20 weeks.	Increased serum HMW adiponectin. These changes correlated significantly with those in eGFR.	Increased eGFR and decreased CRP.
Qu [289]	69 HC patients.	10 mg/day of atorvastatin or rosuvastatin for 12 weeks.	Adiponectin increased from baseline, 11.74 to 13.55 μg/mL (15.4%) with atorvastatin and 9.82 to 16.46 μg/mL (67.6%) with rosuvastatin.	Both statins lowered CRP, MMP-9, PAI-1, TC and LDL-C from baseline. Rosuvastatin lowered TC and LDL-C to a greater extent.
Ando [290]	36 HC patients without known CHD.	Pravastatin or atorvastatin 10 mg/day for 4 months, then switch to the other statin for additional 4 months.	Atorvastatin increased (2.8%) serum adiponectin vs pravastatin. In the whole population: pravastatin from 10.7 to 10.5 μg/mL; atorvastatin from 10.7 to 11 μg/mL.	Atorvastatin significantly reduced TC, LDL-C, TG, CRP and TNF-α, with no benefits on insulin sensitivity. HbA1c increased only in obese patients after atorvastatin.
Kurogi [60]	129 patients with stable CAD, HC and HDL-C < 50 mg/dl.	Pitavastatin 2–4 mg/day or atorvastatin 10–20 mg/day for 30 months.	Pitavastatin increased adiponectin [from 10.14 to 12.79 μg/mL (26.1%)] significantly more than atorvastatin [from 9.07 to 9.74 μg/mL (7.4%)].	Pitavastatin increased HDL-C. Neither statin had a significant effect on HbA1c.
Anagnostis [291]	36 non-diabetic and dyslipidemic patients.	Rosuvastatin 10 mg/day (n = 18) or atorvastatin 20 mg/day (n = 18) for 12 weeks.	No differences in adiponectin levels after 4 and 12 weeks of either statin.	Both statins significantly lowered TC, LDL-C, non-HDL-C and TG. Rosuvastatin significantly reduced insulin and HOMA-IR.
Thongtang [292]	252 hyperlipidemic patients.	Atorvastatin 80 mg/day or rosuvastatin 40 mg/day for 6 weeks.	No significant differences between the 2 groups in adiponectin from baseline (−1.5% atorvastatin vs −4.9% rosuvastatin).	Both statins lowered LDL-C and TG. Rosuvastatin increased HDL-C more than atorvastatin. Both drugs significantly increased CRP and insulin. Atorvastatin increased HbA1c.
Bellia [293]	27 well-controlled T2DM patients.	Rosuvastatin 20 mg/day or simvastatin 20 mg/day for 6 months, then switch to the other statin for additional 6 months.	Both statins did not significantly affect adiponectin levels.	Marked reduction in lipid levels HOMA-IR, leptin, CRP. No changes in insulin sensitivity and significant increase in HbA1c after 12 months with both statins.
Ohashi [294]	238 patients with acute coronary syndrome.	IVUS-guided PCI followed by treatment with pitavastatin and atorvastatin. Follow-up IVUS between 8 and 12 months after PCI.	Adiponectin significantly increased with statin treatment [from 7.8 to 10.3 μg/mL (32%)] at the 8–12 months follow-up. At baseline, adiponectin correlated positively with HDL-C and negatively with TG.	Increase in adiponectin correlated with an increase of HDL-C and decrease of TG.
Koh [295]	43 HC patients.	Placebo, simvastatin 20 mg/day or pravastatin 40 mg/day for 2 months.	Simvastatin significantly decreased plasma adiponectin [from 5.8 to 5.2 μg/mL (−10.3%)], but pravastatin significantly increased it [from 5.6 to 6.1 μg/mL (8.9%)].	Simvastatin and pravastatin significantly improved lipid profile and FMD. Simvastatin significantly increased insulin and leptin.
Kai [296]	27 dyslipidemic patients with mild hypertension.	Initially simvastatin 10 mg/day 6 months or more, then pravastatin 20 mg/day.	The switch simvastatin/pravastatin significantly increased serum adiponectin from 11.9 to 13.1 μg/mL (10.1%), in the absence of differences in LDL-C and blood pressure.	The switch from simvastatin to pravastatin caused little changes in LDL-C and blood pressure, but significantly decreased CRP.
Bellia [297]	29 middle-aged patients with T2DM and mild untreated dyslipidemia.	Rosuvastatin or simvastatin 20 mg/day for 4 weeks.	No changes in adiponectin, fasting glucose and insulin sensitivity in both groups.	Marked reduction of LDL-C. Simvastatin improved FMD better than rosuvastatin.
Tsutamoto [298]	71 stable outpatients with ischemic congestive heart failure, already on standard therapy for the pathology.	Simvastatin 5 mg/day (n = 35) or rosuvastatin 2.5 mg/day (n = 36) for 4 months.	Simvastatin did not change plasma adiponectin, but rosuvastatin significantly increased it from 12.3 to 14.0 μg/mL (13.8%).	oxLDL did not change and HbA1c level slightly increased with simvastatin. Reduction in oxLDL and HbA1c with rosuvastatin.
Nomura [299]	135 hyperlipidemic patients.	Simvastatin 10 mg/day (n = 63), or pitavastatin 2 mg/day (n = 72) for 6 months.	Significant increase in plasma adiponectin with pitavastatin [from 3.53 to 4.36 μg/mL (23.5%)] but not with simvastatin [from 3.51 to 3.59 μg/mL].	According to adiponectin response to pitavastatin, significant decreases of MCP-1 and sCD40L in responders.
Koh [300]	54 HC patients.	Rosuvastatin 10 mg or pravastatin 40 mg/day vs placebo for 2 months.	Rosuvastatin significantly (−9%) decreased, while pravastatin significantly (36%) increased plasma adiponectin.	Rosuvastatin significantly increased HbA1c, fasting insulin and insulin sensitivity. Pravastatin significantly decreased fasting insulin, HbA1c, and insulin sensitivity. Rosuvastatin reduced TC, LDL-C and apo B significantly more than pravastatin.

continued on next page

Table 6
(*continued*)

First author [ref.]	Patients	Drug, duration and dose	Effect on adiponectin	Other effects
Yokoyama [301]	50 patients undergoing surgery for CAD (n = 36) vs valvular heart disease (VHD) (n = 14).	23 patients with CAD and LDL-C > 100 mg/dL were treated with pravastatin 10 mg/day (n = 12) or rosuvastatin 2.5 mg/day (n = 11) for 2 months. 13 patients with CAD and LDL-C < 100 mg/dL and those with VHD without CAD were not treated.	At baseline, adiponectin was lower in CAD vs VHD patients. Pravastatin increased total adiponectin in CAD from 3.28 to 7.16 μg/mL (118%); HMWA from 1.13 to 3.29 μg/mL; MMWA from 1.03 to 1.24 μg/mL; LMWA from 1.37 to 2.15 μg/mL. Rosuvastatin increased total adiponectin from 2.95 to 3.32 μg/mL (12.5%); HMWA from 0.81 to 1.28 μg/mL; MMWA from 0.97 to 0.97 μg/mL; LMWA from 1.03 to 1.34 μg/mL.	Visceral adipose tissue and gene expressions of adiponectin in the pravastatin and VHD groups were similar and higher than in the non-statin and rosuvastatin groups. Protein carbonyl in visceral adipose tissue was lower in pravastatin and VHD vs rosuvastatin and non-statin.
Mita [65]	28 Japanese T2DM and HC patients.	Before entry, rosuvastatin 2.5 mg/day. Then: Group A, pitavastatin 2 mg/day for 12 weeks, then atorvastatin 10 mg/day for 12 weeks. Group B: reverse scheme.	No variations and no differences in adiponectin concentrations.	Similar lipid control with both statins. Pitavastatin significantly lowered glycoalbumin, fasting glucose and insulin resistance vs atorvastatin.

See Table 1 for abbreviations.

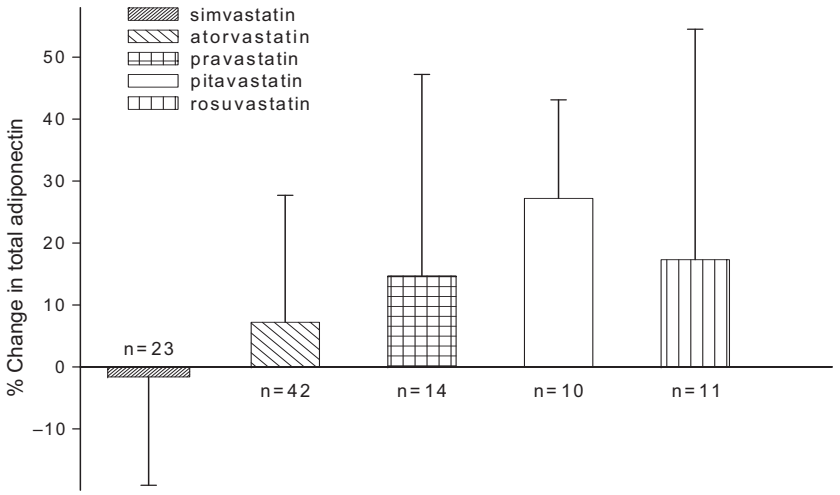

Fig. 3. Effect of different statins on plasma adiponectin. Data are obtained from published clinical studies.

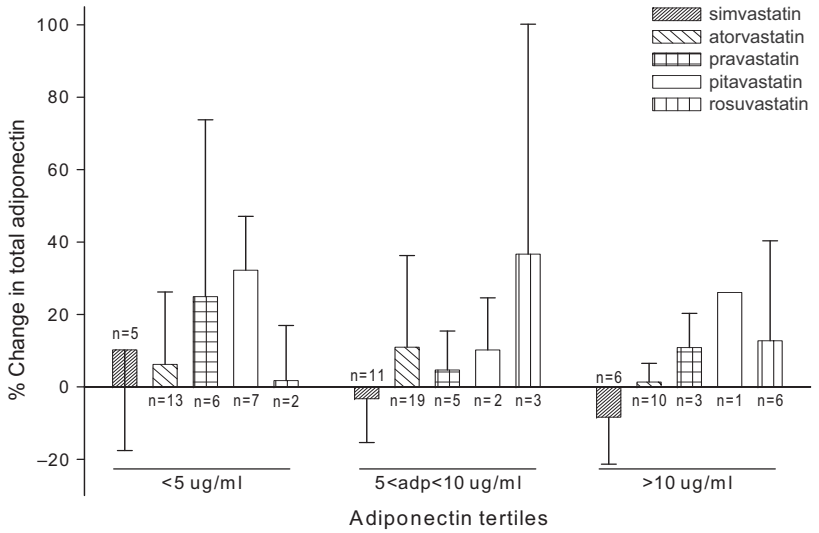

Fig. 4. Effect of different statins depending on basal adiponectin status on plasma adiponectin. Data are obtained from published clinical studies.

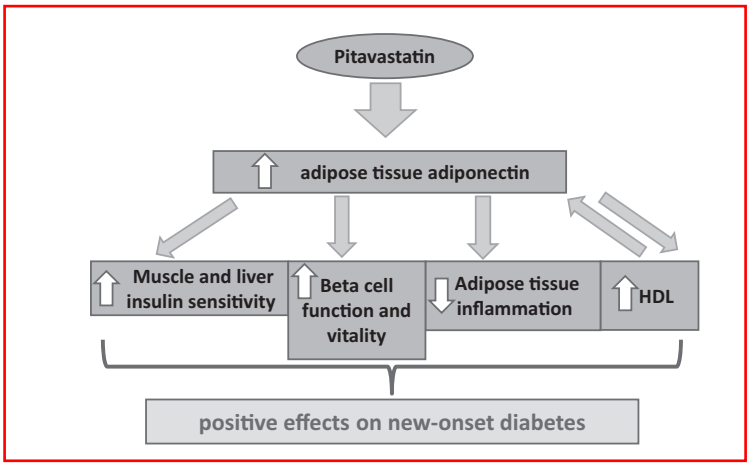

Fig. 5. Possible mechanism of the beneficial effect of pitavastatin on new-onset diabetes.

Box 8. Pitavastatin and HDL-C

- Beneficial effects on HDL-C by pitavastatin are consistent in experimental models and in clinical studies (Table 7).
- In HepG2 cells and rat liver, pitavastatin, but not atorvastatin, increases ABCA1 and plasma HDL, by a PPARα-mediated effect [311].
- Pitavastatin, atorvastatin and simvastatin, but not pravastatin, increase ABCA1 mRNA and ABCA1-mediated efflux to apoA-I in hepatoma cells and rat livers (a PPARα-, γ- and SREBP-2-mediated effect). Only pitavastatin also increases ABCA1 protein by PPARα-mediated ABCA1 stabilization [96,312,313].
- Pitavastatin induces apoAI-dependent cholesterol efflux from slow-turnover adipose tissue pools [63,314].

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Table 7
Clinical studies assessing the effect of pitavastatin on HDL

First author [ref.]	Patients and treatment	Effect
Ishigaki [315]	97 HC and T2DM patients treated with pitavastatin 1–2 mg/day (n = 51) or pravastatin 10 mg/day (n = 46) for 3 years.	Pitavastatin and pravastatin decreased LDL-C (−37.2% vs −25%) and increased HDL-C (5.7% vs 4.5%), while fasting blood glucose increased by 2.2% vs 15.8%, respectively.
Kakuda [316]	129 patients with dyslipidemia treated with atorvastatin 10 mg/day, pitavastatin 2 mg/day or rosuvastatin 2.5 mg/day.	Despite comparable effect on LDL-C lowering, pitavastatin was the most effective in increasing HDL-C and Apo A-I mass.
Miyamoto-Sasaki [317]	30 patients with dyslipidemia treated with pitavastatin 2 mg/day for 4 weeks.	Pitavastatin elevated HDL-C, cholesterol efflux and antioxidant properties of HDL.
Kurogi [60]	129 patients with stable CAD, HC and HDL-C < 50 mg/dl treated for 20 months with pitavastatin or atorvastatin.	Long-term pitavastatin significantly increased ApoAI and HDL-C (20.1%) vs atorvastatin (6.3%).
Ibuki [318]	20 patients (age 66±8 years) previously treated with statins but with HDL-C < 40 mg/dL, switched to pitavastatin (2 mg/day).	Pitavastatin further improved lipid profiles and led to better myocardial protection, possibly via HDL-C elevation.
Teramoto [319]	6,582 patients treated with pitavastatin for 104 weeks.	Pitavastatin significantly increased HDL-C (5.9% in all patients; 24.6% in those with HDL-C < 40 mg/dL at baseline). Elevations in low-HDL-C group 14.0% and 24.9% at 12 and 104 weeks.
Eriksson [48]	330 primary HC or combined dyslipidemic patients and at least two CHD risk factors treated with pitavastatin 4 mg (n = 223) or simvastatin 40 mg (n = 107) for 12 weeks.	Pitavastatin provided a greater increase in HDL-C vs simvastatin.
Gumprecht [49]	279 patients treated with pitavastatin 4 mg or atorvastatin 20 mg (n = 139) daily for 12 weeks. Treatment continued for further 44 weeks if lipid targets not reached at week 8.	No significant changes between patients treated with pitavastatin or atorvastatin.
Maruyama [320]	743 consecutive patients who underwent PCI retrospectively investigated.	Atorvastatin or pitavastatin significantly reduced LDL-C compared with pravastatin or no statin. Only pitavastatin treatment significantly increased HDL-C (13.4%).
Shimabukuro [53]	Patients with T2DM, HC and/or HTG treated with pitavastatin 2 mg (n = 16) or atorvastatin 10 mg (n = 15) for 6 months.	HDL-C increased after 1, 3 and 6 months of pitavastatin, whereas it even decreased after 6 months of atorvastatin. Pitavastatin increased cholesterol of medium HDL subclass.
Yanagi [54]	90 Japanese patients with T2DM and hyperlipidemia treated with rosuvastatin 2.5 mg/day or pitavastatin 2 mg/day	Rosuvastatin had a more potent LDL-C-lowering and CRP-lowering effect compared with pitavastatin. Both statins lowered TG and increased HDL-C.
Fujioka [321]	83 patients treated with pitavastatin 1–2 mg/day for 12 months.	Pitavastatin significantly reduced TC and LDL-C (18.3% and 30.1%). HDL-C levels significantly increased at 6 months (11.9%).
Ose [322]	1,353 patients with primary HC or combined dyslipidemia treated with pitavastatin 4 mg/day for up to 52 weeks.	HDL-C levels rose continually during follow up, increasing by 14.3% over baseline.
Teramoto [323]	20,279 HC patients treated with pitavastatin for 104 weeks.	In time-course analysis, HDL-C in patients with low HDL-C increased continuously (14.0% and 24.9% at 12 and 104 weeks, respectively).
Motomura [56]	65 Japanese T2DM patients were administered pitavastatin 2 mg/day and completed a 6-month follow-up.	HDL-C significantly increased after 1 month and remained at the higher level for 6 months.
Fukutomi [324]	43 HC patients with low HDL-C treated with pitavastatin for 12 months.	Pitavastatin significantly and persistently increased HDL-C (from 36.0 to 40.5 mg/dL) and apoA-I (from 108.4 to 118.7 mg/dL).
Koshiyama [58]	178 Japanese HC patients (103 with T2DM) treated with pitavastatin 12 mg/day for 12 months.	Serum HDL-C levels significantly increased.
Sasaki [59]	88 Japanese patients with elevated LDL-C and glucose intolerance treated with pitavastatin 2 mg/day and 85 with atorvastatin 10 mg/day for 52 weeks.	Change in HDL-C was significantly greater after pitavastatin vs atorvastatin (8.2% vs 2.9%). Similar changes in ApoA-I (5.1% vs 0.6%).
Yokote [325]	Japanese patients with TC ⩾220 mg/dL received pitavastatin 2 mg (n = 126) or atorvastatin 10 mg (n = 125) for 12 weeks.	HDL-C increased after 12 weeks with pitavastatin (3.2%) but not with atorvastatin.
Kawano [326]	29 HC patients treated with pitavastatin 2 mg/day for 4 weeks.	HDL-C and HDL(2)-C increased significantly by 6.0% and 9.0%, with no change in HDL(3)-C. While Prebeta 1-HDL decreased significantly (−8.7%), its disappearance rate increased significantly (13.0%). Pitavastatin may promote early steps of reverse cholesterol transport.
Lee [327]	222 Korean patients treated with pitavastatin 2 mg/day or atorvastatin 10 mg/day. Patients not at LDL-C goal by week 4 received a double dose of the drug for additional 4 weeks.	No significant differences between groups in LDL-C, TC, TG and HDL-C.
Yoshitomi [328]	137 HC patients treated with pitavastatin or atorvastatin.	No significant differences between the groups in TC, LDL-C and HDL-C.
Park [329]	49 Korean patients treated with pitavastatin 2 mg/day and 46 with simvastatin 20 mg/day for 8 weeks.	Pitavastatin was non-inferior to simvastatin in terms of reducing LDL-C, TC and TG and increasing HDL-C.
Saito [330]	240 patients received pitavastatin 2 mg/day or pravastatin 10 mg/day for 12 weeks.	Pitavastatin significantly lowered LDL-C (−37.6%) vs pravastatin (−18.4%). Pitavastatin also significantly reduced TG, apo B, C-II and C-III, compared with pravastatin, and increased HDL-C, apo A-I and A-II, to the same extent as pravastatin.

See Table 1 for abbreviations.

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