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Adiponectin plasma levels are increased by atorvastatin treatment in subjects at high cardiovascular risk

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Abstract

Adiponectin can suppress atherogenesis by inhibiting the adherence of monocytes, reducing their phagocytic activity, and suppressing the accumulation of modified lipoproteins in the vascular wall. Contradictory data have been reported about the effect of statins on adiponectin plasma levels. In this work, adiponectin plasma levels were measured in 102 statin-free subjects from the Spanish population of the Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (ACTFAST) study, a 12-week, prospective, multi-centre, open-label trial which enrolled subjects with coronary heart disease, coronary heart disease-equivalent or a 10-year coronary heart disease risk >20%. Subjects were assigned to atorvastatin (10–80 mg/day) based on low-density lipoprotein (LDL)-cholesterol concentration at screening. For comparison, age and gender-matched blood donors (N=40) were used as controls. Control subjects did not present hypertension, hypercholesterolemia, diabetes, metabolic syndrome and history of cardiovascular diseases. Adiponectin levels were diminished in patients at high cardiovascular risk compared with control subjects [4166 (3661–4740) vs 5806 (4764–7075) ng/ml respectively; geometric mean (95% CI); P<0.0001]. In the whole population, atorvastatin treatment increased adiponectin levels [9.7 (3.2–16.7);% Change (95% CI); P=0.003]. This increment was in a dose-dependent manner; maximal effect observed with atorvastatin 80 mg/d [24.7 (5.7–47.1); P=0.01]. Adiponectin concentrations were positively correlated with high-density lipoprotein-cholesterol both before and after atorvastatin treatment. No association was observed between adiponectin and LDL-cholesterol before and after atorvastatin treatment. In conclusion, atorvastatin increased adiponectin plasma levels in subjects at high cardiovascular risk, revealing a novel anti-inflammatory effect of this drug.

Keywords: Cholesterol-lowering drugs; High cardiovascular risk; Inflammation; Adiponectin

1. Introduction

Obesity and insulin resistance are associated with cardiovascular risk factors, including altered levels of inflammatory markers and endothelial dysfunction (Weyer et al., 2002).

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Studies have demonstrated that adipocytes synthesize and secrete a number of biologically active molecules so called adipokines, including leptin, tumor necrosis factor, interleukin-6, resistin and adiponectin (Lyon et al., 2003). Adiponectin is an adipocyte-specific plasma protein, which is an anti-inflammatory and anti-atherosclerotic cytokine (Han et al., 2007). In this respect, adiponectin diminishes the expression of adhesion molecules in endothelial cells (Ouchi et al., 1999), suppresses macrophage to foam cell transformation (Ouchi et al., 2001) and inhibits smooth muscle cells proliferation and migration (Arita et al., 2002). Plasma levels of adiponectin are decreased in subjects with dyslipidemia (Matsubara et al., 2002) or coronary artery disease and hypoadiponectinemia is independently associated with coronary artery disease even after adjustment for several coronary risk factors (Kumada et al., 2003). Moreover, adiponectin plasma concentrations can be used to assess the risk of coronary artery disease and may be related to the development of acute coronary syndrome (Nakamura et al., 2004). Plasma levels of adiponectin are also associated with coronary lesion complexity in men with coronary artery disease (Otsuka et al., 2006). Although the mechanisms underlying the anti-inflammatory properties of adiponectin are not well understood, its anti-inflammatory and anti-atherogenic properties may be related, at least in part, to its ability to stimulate production of nitric oxide from vascular endothelium (Chen et al., 2003).

Several trials have verified that 3-hydroxy-3-methyl-glutaryl Coenzyme A (HMG-CoA) reductase inhibitor (statin) therapy lowers the risk of cardiovascular events by reducing plasma cholesterol levels (Baigent et al., 2005), and practice guidelines for high cardiovascular risk patients describe the importance of reaching low-density lipoprotein (LDL)-cholesterol (Expert panel., 2001). The Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (ACTFAST) study included patients with coronary heart disease, coronary heart disease-equivalent (defined as diabetes, peripheral vascular disease or cerebrovascular disease) or a 10-year coronary heart disease risk >20% and was designed to determine whether using atorvastatin at starting doses appropriate for the degree of LDL-cholesterol reduction required would achieve LDL-cholesterol targets quickly with either no titration or just one titration step (Martineau et al., 2007).

Adiponectin plasma levels are associated with an increased risk to develop an acute coronary syndrome and with prevalence of coronary artery disease. Since statins have demonstrated beneficial effects in the treatment of cardiovascular diseases, we have analyzed whether atorvastatin treatment modifies adiponectin plasma levels in the subset of Spanish statin-free subjects who took part in ACTFAST.

2. Methods

2.1. Study design

The study design of ACTFAST has been described in detail elsewhere and is only summarized here (Martineau et al., 2007). The ACTFAST study is a 12-week, prospective, multicenter, open-label trial which enrolled subjects (either statin-free or statin-treated at baseline) with coronary heart disease, a coronary heart disease-equivalent (defined as diabetes, peripheral vascular disease or cerebrovascular disease) or a 10-year coronary heart disease risk >20%. In addition, subjects had to present with a LDL-cholesterol >2.6 mmol/L and ≤5.7 mmol/L, as well as triglycerides ≤6.8 mmol/L and had to be willing to follow the NCEP III multifaceted lifestyle approach (or local equivalent).

The Institutional review board of all participating centers approved the ACTFAST study protocol and all participants provided written informed consent. This study was conducted in compliance with the ethical principles of the Declaration of Helsinki.

For comparison, age and gender-matched blood donors (N=40) were used as controls. Control subjects did not present with hypertension, hypercholesterolemia, diabetes, the metabolic syndrome and history of cardiovascular diseases at the time of blood sampling.

2.2. Dose assignment

Subjects were assigned to a starting dose of atorvastatin (10–80 mg/day) based on LDL-cholesterol at screening (100–149; 150–159; 160–169 and 170–220 mg/dl were assigned to 10, 20, 40 or 80 mg/day, respectively). After 6 weeks, if not already at maximum dose, subjects not reaching LDL-cholesterol target (<100 mg/dl) had their dose doubled. Subjects initially allocated to atorvastatin 80 mg/day who did not reach LDL-cholesterol targets, were continued on that dose and a more intense therapeutic lifestyle intervention (NECP step II diet or equivalent) was recommended.

2.3. Laboratory determinations

As part of the main protocol, fasting venous blood samples were collected into tubes with EDTA anticoagulant at baseline and at 12 weeks. Plasma was isolated by low speed centrifugation and shipped to a core laboratory for storage at −70 ° C. The paired baseline and 12-week samples were then shipped to the laboratory (Madrid, Spain) and measured in batches. Soluble adiponectin concentrations were measured with commercially available enzyme-linked immuno-sorbent assay (ELISA) kits (R&D Systems, Minneapolis, USA). For high sensitivity C-Reactive Protein (hs-CRP) measurement whole venous blood was collected in tubes without anticoagulant and centrifuged at room temperature. Serum CRP was assessed with a high-sensitivity, latex microparticle-enhanced immunoturbidimetric assay (Tina-Quant; Roche Diagnostics GmbH, Penzberg, Germany).

The minimum detectable concentration of soluble adiponectin and hs-CRP were 0.246 ng/ml and 0.03 mg/l respectively. Intra-assay and inter-assay coefficients of variation were 3.6%–6.4% (soluble adiponectin) and 1.3% and 5.7% (hs-CRP).

2.4. Statistical analysis

The ACTFAST study enrolled 2,117 subjects (either statin-free or statin-treated at baseline) with coronary heart disease or a

coronary heart disease-equivalent. Of the 2,117 subjects, 102 (statin-free) were included in the Spanish sub-population of the ACTFAST study. As expected, the distributions of the inflammatory markers were skewed. To meet the distributional assumptions of the statistical models, the markers were log-transformed for the statistical models and antilog-transformed for descriptive purposes, yielding geometric means and 95% confidence intervals (CI) for baseline, week-12 concentrations, and the change in concentrations over the study period. The pre-specified primary endpoint was the effect of atorvastatin 10, 20, 40 and 80 mg on decreasing adiponectin levels over the 12-week study period. The primary endpoint was assessed by ANCOVA, adjusted for the initial level of the marker. Secondary endpoints included the effect of atorvastatin on the changes of the adiponectin levels over 12 weeks, according to the presence of diabetes or metabolic syndrome [definition of metabolic syndrome according to NCEP-III: When 3 or more of the following are present: waist circumference > 102 cm in men or > 88 cm in women; triglycerides ≥ 150 mg/dl (1.7 mmol/l); high-density lipoproteins (HDL)-cholesterol <40 mg/dl (1.0 mmol/l) in men, <50 mg/dl (1.3 mmol/l) in women; blood pressure ≥ 130/≥ 85 mm Hg, and FPG ≥ 110 mg/dl (6.1 mmol/l)] (Expert panel., 2001).

Data were analyzed on an intention-to-treat and per-protocol basis. The intention-to-treat population consisted of all subjects who were assigned a starting dose, took at least one dose of study medication, and who had at least one subsequent assessment. The per-protocol population consisted of those intention-to-treat subjects who completed the study as per-protocol, were exempt of major protocol violations and who were compliant with study treatment.

The per-protocol population excluded subjects with a baseline hsCRP > 10 mg/l and those presenting an acute inflammatory, infectious or traumatic event at the time of blood sampling. Subjects using systemic anti-inflammatory or immuno-modulating drugs [e.g. NSAIDS, Cox2 inhibitors, corticosteroids, cytotoxic agents, thiazolididione, with the exception of low doses of acetylsalicylic acid (≤ 325 mg/day)] for more than 10 days during any treatment period or within 10 days of a laboratory assessment were also excluded from the per-protocol analysis of inflammatory markers.

Post-hoc analyses were designed to analyze the differences between adiponectin concentrations in subjects at high cardiovascular risk and control subjects. The association between adiponectin (log-transformed) versus continuous variables was explored using Pearson correlation coefficients, without adjustment for doses used. Statistical significance was defined as a value of $P<0.05$.

3. Results

3.1. Adiponectin plasma levels are diminished in subjects at high cardiovascular risk

The baseline characteristics of the intention-to-treat population included in the Spanish population are summarized in Table 1. We have studied soluble adiponectin plasma concentrations of statin-free high risk subjects enrolled in the Spanish population of the ACTFAST study and compared with those in age and gender-matched control subjects. Post-hoc analyses showed that adiponectin levels were diminished in subjects at high cardiovascular risk compared to control subjects [4134 (3673–4652) vs 5806 (4764–7075) ng/ml; Geometric mean (95% CI), respectively; $P=0.005$].

When soluble adiponectin was considered as a continuous variable, we observed that soluble adiponectin was positively associated with HDL-cholesterol (Fig. 1A) and negatively with triglycerides or total cholesterol/HDL-cholesterol (Table 2). In contrast, soluble adiponectin was not correlated with total cholesterol or LDL-cholesterol.

Using a univariate analyses, baseline adiponectin plasma levels were analyzed according with the presence of diabetes or the metabolic syndrome (pre-specified subgroups). No differences were observed in adiponectin concentrations in subjects

Table 1
Baseline characteristics of the intent-to-treat study population

Variable	Atorvastatin 10 mg	Atorvastatin 20 mg	Atorvastatin 40 mg	Atorvastatin 80 mg	Overall
Mean (SD) or *N* (%)	(*N*=53)	(*N*=14)	(*N*=9)	(*N*=26)	(*N*=102)
Age, y	65.1 (10.2)	64.7 (9.3)	63.4 (9.7)	60.7 (10.1)	63.8 (10)
Weight, kg	75.5 (10.4)	79.8 (10.9)	6.1 (10.4)	79 (11.4)	77 (10.7)
Body mass index*	28.2 (3.4)	27.6 (3)	29 (3.7)	29.2 (3.8)	28.7 (4)
Men	39 (73.6)	12 (85.7)	5 (55.6)	20 (76.9)	76 (74.5)
White	53 (100)	14 (100)	9 (100)	26 (100)	102 (100)
Smoking status					
Current smoker	5 (9.4)	2 (14.3)	2 (22.2)	5 (19.2)	14 (13.7)
Past or nonsmoker	48 (90.6)	12 (85.7)	7 (77.8)	17 (77.8)	88 (86.3)
Alcohol consumption	22 (41.5)	9 (64.3)	4 (44.4)	16 (61.5)	51 (50)
History of hypertension	34 (64.2)	7 (50)	8 (88.9)	14 (53.8)	63 (61.8)
History of diabetes mellitus	10 (18.9)	1 (7.1)	2 (22.2)	10 (38.5)	23 (22.5)
Metabolic syndrome	35 (66)	8 (57.1)	4 (44.4)	11 (42.3)	58 (56.9)
History of cerebrovascular disease	4 (7.6)	3 (21.4)	1 (11.1)	1 (3.9)	9 (8.8)
History of peripheral vascular disease	7 (13.2)	0 (0)	0 (0)	1 (3.9)	8 (7.8)
History of coronary artery disease	48 (90.6)	11 (78.6)	4 (44.4)	20 (76.9)	83 (81.4)

*Calculated as weight in kilograms divided by the square of the height in meters.
Results are expressed as number of subjects (percentage) or mean (standard deviation).

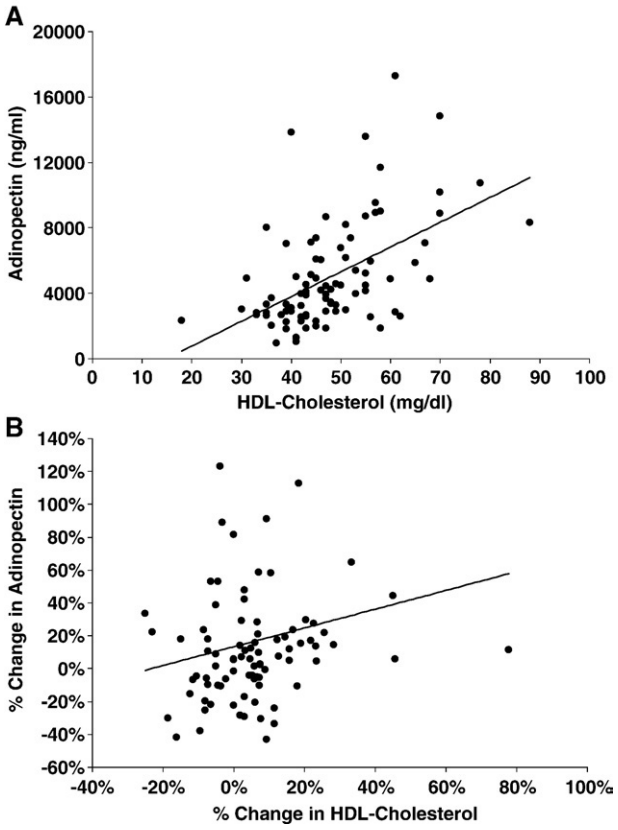

Fig. 1. Correlations (Pearson rank) between (A) adiponectin plasma levels and HDL-cholesterol at baseline and between (B) % change adiponectin and % change HDL-cholesterol after atorvastatin treatment in subjects at high cardiovascular risk.

with diabetes compared with those without diabetes [4060 (3152–5229) vs 4200 (3602–4896) ng/ml; $P=0.83$]. In addition, no differences were also observed in adiponectin plasma levels in subjects with the metabolic syndrome compared with those without the metabolic syndrome [4092 (3415–4903) vs 4223 (3504–5089); $P=0.81$].

3.2. Effects of atorvastatin treatment on soluble adiponectin plasma levels

At baseline, 53%, 14%, 10% and 23% of subjects were assigned to 10, 20, 40 and 80 mg, respectively. As expected, atorvastatin treatment significantly decreased total cholesterol [223 (217–230) to 156 (148–164) mg/dl; $P<0.0001$], LDL-cholesterol [149 (144–154) to 84 (81–88) mg/dl; $P<0.0001$], triglycerides [131 (119–144) to 110 mg/dl (96–127); $P=0.001$], ApoB [1.1 (1.1–1.1) vs 0.7 (0.7–0.7) g/l; $P<0.0001$] and total cholesterol/HDL-cholesterol ratio [4.8 (4.5–5) to 3.2 (3–3.3); $P<0.0001$] and increased HDL-cholesterol [47 (44–49) to 49 (47–51) mg/dl; $P=0.002$].

The effect of atorvastatin on soluble adiponectin is shown in Fig. 2A. In the whole population, atorvastatin increased circulating adiponectin concentrations in subjects at high cardiovascular risk. When we analyzed the effect of the different atorvastatin doses used, we observed that all doses augmented soluble adiponectin concentrations, and this was statistically

Table 2
Baseline and at follow-up correlations between continuous variables and Adiponectin

	Soluble Adiponectin at baseline Correlation Coefficient	*P* value	Soluble Adiponectin at follow-up Correlation Coefficient	*P* value
Total Cholesterol	0.09		0.08	
		0.38		0.46
LDL-cholesterol	0.01		−0.16	
		0.92		0.13
HDL-cholesterol	0.52		0.23	
		<0.0001		0.03
Triglycerides	−0.25		0.2	
		0.02		0.06
Total Cholesterol/ HDL-cholesterol	−0.37		−0.06	
		0.0003		0.56
Hs-CRP	0.14		−0.06	
		0.2		0.54

Correlations and *P*-values from Pearson Correlation coefficient.

significant for atorvastatin 40 and 80 mg/day (Fig. 2B). The per-protocol analysis confirmed the intention-to-treat results (Fig. 2B).

Additional post-hoc analyses were designed to assess whether the observed atorvastatin-induced changes in soluble adiponectin were related to atorvastatin-induced changes in lipid parameters. We found a small but statistically significant association between percentage change in soluble adiponectin and percentage change observed in HDL-cholesterol (Fig. 1B). No evidence of association between percentage change in soluble adiponectin and percentage change in total cholesterol,

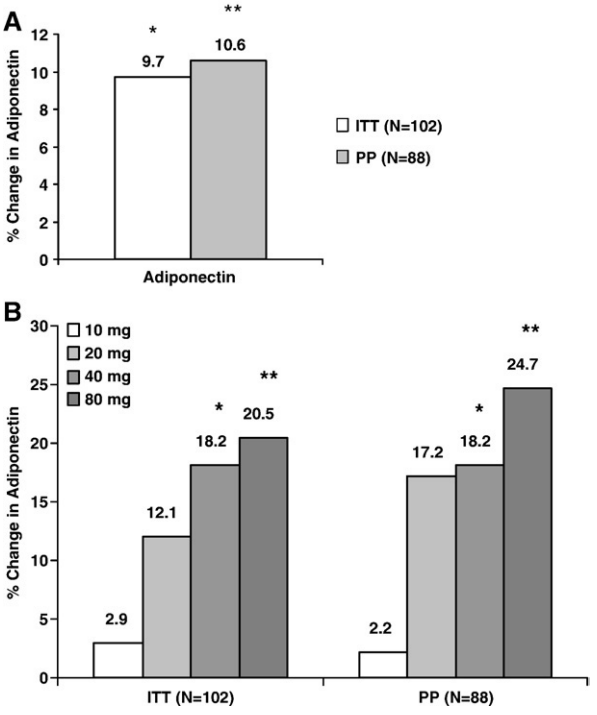

Fig. 2. Effect of atorvastatin on soluble adiponectin plasma concentrations in subjects at high cardiovascular risk. A) Effect of atorvastatin on soluble adiponectin in the whole population. *$P=0.003$; **$P=0.004$. B) Effect of all atorvastatin doses on soluble adiponectin concentrations. *$P=0.02$; **$P=0.01$. Probability values from paired *t*-test.

LDL-cholesterol, triglycerides or total cholesterol / HDL-cholesterol ratio was noted (Table 2).

Treatment with atorvastatin increased circulating soluble adiponectin in subjects without diabetes [4200 (3602–4896) vs 4619 (3918–5445) ng/ml; $P=0.01$; geometric mean (95% CI) before and after treatment respectively] or without the metabolic syndrome [4223 (3504–5089) vs 4693 (3838–5739) ng/ml; $P=0.02$]. However, atorvastatin was less effective in augmenting soluble adiponectin in subjects with diabetes compared with those without diabetes [4060 (3152–5229) vs 4565 (3446–6048) ng/ml; $P=0.13$; respectively] or with the metabolic syndrome compared with those without the metabolic syndrome [4092 (3415–4903) vs 4494 (3696–5464) ng/ml; $P=0.08$; respectively].

As expected, all doses of atorvastatin diminished CRP concentrations, although only atorvastatin 40–80 mg/d were statistically significant [−11 (−30.7, 14.2), $P=0.35$; −15.2 (−54.2, 57), $P=0.57$; −49.1 (−64.6, −26.7), $P=0.003$; −48.3 (−63.5, −26.7), $P=0.0006$; for 10, 20, 40, and 80 mg/day, respectively; % change (95% CI)). Furthermore, we found no evidence of association between the percentage change observed in CRP and the percentage change in soluble adiponectin ($r=-0.06$, $P=0.54$) in the whole population.

4. Discussion

Our data indicate that soluble adiponectin is diminished in subjects at high cardiovascular risk compared with control subjects. In addition, our results also demonstrate that atorvastatin increases soluble adiponectin levels in a dose-dependent manner.

These results could be clinically relevant for different reasons. Several studies have proposed that soluble adiponectin plasma levels are associated with cardiovascular diseases (Matsubara et al., 2002; Kumada et al., 2003; Nakamura et al., 2004; Otsuka et al., 2006). Decreased plasma adiponectin levels are observed in patients with type 2 diabetes, hypertension, metabolic syndrome, and coronary artery disease (Weyer et al., 2001; Iwashima et al., 2004; Hotta et al., 2000). In this respect, we have observed that adiponectin concentrations are diminished in subjects at high cardiovascular risk compared with control subjects. Furthermore, our results are in agreement with previous studies in which adiponectin is diminished around 30% in subjects with coronary artery disease compared with healthy blood donors (Kumada et al., 2003). Furthermore, this diminution is associated with a 2-fold increase of coronary artery disease prevalence suggesting that low levels of adiponectin concentrations observed in our subjects conferred an increased of risk. We have not found differences in adiponectin plasma levels between subjects with diabetes or the metabolic syndrome when compared with subjects without these pathologies. In this respect, it is important to note that both patients without diabetes or the metabolic syndrome were included in this study with a similar cardiovascular risk (presence of coronary heart disease, coronary heart disease-equivalent or 10-year coronary heart disease risk >20%), which should affect the adiponectin concentrations. In this context, our results are in agreement with data reported on another inflammatory marker, the soluble monocyte chemoatractant protein 1, which was not increased in subjects with type 2 diabetes mellitus compared with those without diabetes but with history of cardiovascular disease (Blaha et al., 2006).

Secondly, atorvastatin increased soluble adiponectin concentration in a dose-dependent manner with a maximal effect observed with 80 mg/day. Contradictory data have been reported about the effect of statin treatment on soluble adiponectin plasma levels. It has been reported that simvastatin 20 mg/day did not change soluble adiponectin plasma levels in hypercholesterolemic, hypertensive subjects at 2 months (Koh et al., 2004). Moreover, atorvastatin 10 mg/day did not alter adiponectin concentrations in subjects with combined hyperlipidemia (Koh et al., 2005). However, Nakamura et al. have recently reported that atorvastatin 10 mg/day increase adiponectin plasma levels in subjects with coronary artery disease and hyperlipidemia (Nakamura et al., 2007). Our results are agreement with the observation that 10–20 mg/day of atorvastatin did not significantly modify soluble adiponectin plasma concentrations. In contrast, 40–80 mg/day atorvastatin increased adiponectin concentrations in subjects at high cardiovascular risk, indicating that the effect induced by short-term treatment with statins depends of the dose used. Furthermore, it is important to note that 40–80 mg/day of atorvastatin practically normalized adiponectin plasma levels in subjects at high cardiovascular risk compared with levels observed in healthy subjects.

The mechanism by which atorvastatin increases adiponectin concentrations is unknown. We have observed that adiponectin concentrations are associated positively with HDL-cholesterol and negatively with triglycerides and cholesterol/HDL-cholesterol at baseline. However, after treatment, only a minimal association with HDL-cholesterol was observed. These results may indicate that the effect observed on adiponectin plasma levels after atorvastatin treatment was independent of the effect observed on lipid parameters. In this respect, statins have been shown to provide clinical benefit in reducing cardiovascular events, even in subjects without elevated LDL-cholesterol, raising the possibility that the benefit may be due to effects beyond changes in plasma lipoproteins (Liao and Laufs, 2005). However, it cannot be excluded that the effect observed with atorvastatin in our study could be also related to the lipid lowering properties of statins. Other potential mechanism is the relation existing between adiponectin expression and some proinflammatory cytokines. For example, It is known that tumor necrosis factor (TNF) can modulate the expression of different adipokines including the diminution of adiponectin secretion by adipocytes (Ahn et al., 2007), and TNF expression is negatively associated with adiponectin within human coronary atherosclerotic plaques (Karaduman et al., 2006). In this regard, TNF plasma concentrations are increased in subjects with coronary artery disease (Mizia-Stec et al., 2003). Furthermore, it has been demonstrated that atorvastatin can diminish TNF expression and secretion and reduce TNF plasma levels in subjects with hypercholesterolemia (Ascer et al., 2004). In this context, it is possible that an increased expression of proinflammatory cytokines could be associated with a diminution of adiponectin secretion in subjects at high cardiovascular risk and that atorvastatin

treatment increases adiponectin plasma levels through a reduction of other/s proinflammatory cytokines, indicating that atorvastatin treatment could have a novel anti-inflammatory effect through the normalization of adiponectin expression.

It is important to note that the diminution observed in CRP, a more established inflammatory marker, was similar to the increment noted in adiponectin plasma levels. However, no association was observed between CRP and adiponectin concentrations before and after treatment with atorvastatin, indicating an independent effect of statins on adiponectin. In this respect, different studies have demonstrated that adiponectin is negatively associated with CRP concentrations (Ouchi et al., 2003b). It is possible that the absence of association between adiponectin and CRP is due to a small simple size of the studied population.

Although this study was not designed to compare the effect of atorvastatin with other anti-inflammatory drugs, it is known that some drugs with anti-inflammatory properties can modulate circulating adiponectin levels. In this respect, therapy with thiazolidinediones has demonstrated to increase adiponectin plasma concentrations. In particular, rosiglitazone increased adiponectin levels in subjects with type 2 diabetes (Chu et al., 2006) or in subjects with metabolic syndrome (Esposito et al., 2006) and pioglitazone augmented adiponectin levels in subjects with type 2 diabetes (Araki et al., 2006) and in non-diabetic subjects at cardiovascular risk (Forst et al., 2007). Furthermore, antihypertensive drugs such as ramipril or candesartan can also increase adiponectin plasma concentrations in hypertensive patients (Koh et al., 2007). Finally, another peroxisome proliferator-activated receptor ligand, bezafibrate also augmented adiponectin levels in subjects with coronary heart disease (Hiuge et al., 2007).

Thirdly, the importance of the increment of adiponectin plasma concentrations associated to atorvastatin treatment is due to the fact that this protein has several beneficial effects on the arterial wall (Ouchi et al., 2000). Adiponectin reduces expression of adhesion molecules in endothelial cells and decreases cytokine production from macrophages (Liao and Laufs, 2005; Ouchi et al., 2000). Furthermore, adiponectin induces production of the anti-inflammatory mediator interleukin 10 (Wolf et al., 2004). Moreover, adiponectin supressess proliferation and migration induced by platelet-derived growth factor in smooth muscle cells (Arita et al., 2002) and inhibits metalloproteinase activity in human monocyte-derived macrophages (Kumada et al., 2004). In addition, endothelium-dependent vasodilation in response to acetylcholine is significantly reduced in adiponectin-knockout mice (Ouchi et al., 2003a) and increasing adiponectin levels using adenoviral vector attenuated neointimal formation and cell proliferation in balloon injured arteries in adiponectin-deficient mice (Matsuda et al., 2002). Finally, elevated adiponectin plasma levels diminished atherosclerosis in ApoE knockout mice (Okamoto et al., 2002). All these data may indicate that high levels of adiponectin protect to atherosclerotic plaque development.

This study has some limitations, including a small simple size, the dose groups were of unequal size and the study lacked an untreated control group, due to ethical considerations. In particular the small number of patients involved in our study could affect correlations. This study was not designed to analyze cardiovascular events due to the short period of follow-up. Therefore we cannot analyze the association between soluble adiponectin concentrations, atorvastatin treatment and cardiovascular events. More studies analyzing the effect of statins on adiponectin plasma levels in large populations are warranted.

5. Conclusions

In summary, this study confirms that soluble adiponectin is decreased in subjects at high cardiovascular risk. More importantly, our results provide evidence that atorvastatin increases soluble adiponectin plasma levels in subjects at high cardiovascular risk, indicating that short-term treatment with atorvastatin exhibits anti-inflammatory effects in subjects at high cardiovascular risk.

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