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Improved endothelial function with simvastatin but unchanged insulin sensitivity with simvastatin or ezetimibe

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Abstract

In addition to their expected effects on lipid profile, lipid-lowering agents may reduce cardiovascular events because of effects on nonclassic risk factors such as insulin resistance and inflammation. Ezetimibe specifically blocks the absorption of dietary and biliary cholesterol as well as plant sterols. Although it is known that an additional reduction of low-density lipoprotein cholesterol (LDL-C) levels can be induced by the combination of ezetimibe with statins, it is not known if this can enhance some pleiotropic effects, which may be useful in slowing the atherosclerotic process. This study assessed the effects of simvastatin and ezetimibe, in monotherapy or in combination, on markers of endothelial function and insulin sensitivity. Fifty prediabetic subjects with normo- or mild-to-moderate hypercholesterolemia were randomly allocated to 2 groups receiving either ezetimibe (10 mg/d) or simvastatin (20 mg/d) for 12 weeks, after which the drugs were combined for both groups for an additional 12-week period. Clinical and laboratory parameters were measured at baseline and after 12 and 24 weeks of therapy. Homeostasis model assessment of insulin resistance index and the area under the curve of insulin were calculated. As expected, both groups receiving drugs in isolation significantly reduced total cholesterol, LDL-C, apolipoprotein B, and triglyceride levels; and additional reductions were found after the combination period ($P < .05$). After 12 weeks of monotherapy, plasminogen activator inhibitor–1 levels and urinary albumin excretion were lower in the simvastatin than in the ezetimibe group. No change in homeostasis model assessment of insulin resistance index, area under the curve of insulin, and adiponectin levels was observed after either the monotherapies or the combined therapy. However, simvastatin combined with ezetimibe provoked significant reductions in E-selectin and intravascular cellular adhesion molecule–1 levels that were independent of LDL-C changes. Our findings support claims that simvastatin may be beneficial in preserving endothelial function in prediabetic subjects with normo- or mild-to-moderate hypercholesterolemia. Alternatively, a deleterious effect of ezetimibe on the endothelial function is suggested, considering the increase in intravascular cellular adhesion molecule–1 and E-selectin levels. Simvastatin and ezetimibe, in isolation or in combination, do not interfere with insulin sensitivity.

1. Introduction

Disorders of metabolic homeostasis, including glucose intolerance and dyslipidemia, are characterized by insulin resistance and frequently cluster with endothelial dysfunction [1]. Despite substantial evidence suggesting a potential role for endothelial dysfunction in insulin resistance, such a relationship is probably bidirectional [2]. As subjects with multiple metabolic disturbances are at high cardiovascular risk, they should be aggressively treated to minimize this risk. Benefits of lipid-lowering therapy are mainly attributed to its effects on lipid profile, but pleiotropic effects are also postulated [3,21]. Statins have been shown to attenuate low-grade inflammation [4] that is considered part of insulin resistance syndrome [5]. The effects of these agents on insulin sensitivity are controversial because different types of statin have been used, at different doses, and different indices in literature have been used to assess glucose metabolism. Some authors have observed that some statins improve glucose metabolism in several populations [6-11]; but others have reported that these drugs, particularly simvastatin and atorvastatin, either do not change or, in fact, worsen insulin sensitivity in patients with metabolic syndrome or type 2 diabetes mellitus [10,12-15].

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Plasma adiponectin levels have been inversely correlated with insulin resistance and subsequent diabetes [16] and may represent a link between metabolic signals, inflammation, and atherosclerosis [1]. Although few studies with atorvastatin or simvastatin have shown increases in adiponectin levels, there is no current consensus [3,13,15,17,18]. The effect of ezetimibe on this hormone concentration has been little studied [17].

It is well known that ezetimibe added to statin therapy increases the reduction in low-density lipoprotein cholesterol (LDL-C) levels [19,20]. However, whether such combination of lipid-lowering agents is beneficial with regard to pleiotropic effects is not clear. Scarce data are available regarding the effects of the statin-ezetimibe combination on glucose metabolism [11].

Favorable effects of statins in endothelial function have also been described [21]. Circulating biomarkers produced by endothelium, such as intravascular cellular adhesion molecule–1 (ICAM-1), E-selectin, and plasminogen activator inhibitor–1 (PAI-1), have been used to investigate endothelial dysfunction and are associated with risk of cardiovascular events [22-24]. Furthermore, increased urinary albumin excretion (UAE) is considered a marker of systemic endothelial dysfunction and predicts cardiovascular mortality in populations [25-27]. The role for statins in the amelioration of these biomarkers is a matter of controversy [23-25,28-35]. Some findings suggest that statins may have beneficial effects on diminishing PAI-1, but other investigations have failed to find these benefits [32-35]. No data concerning the effect of the statin-ezetimibe combination is available.

Therefore, we investigated whether simvastatin and ezetimibe, in monotherapy or in combination, have beneficial effects on insulin sensitivity and markers of endothelial function and coagulation process in prediabetic subjects with normo- or mild-to-moderate hypercholesterolemia.

2. Subjects and methods

Participants were screened from outpatient clinics at the Federal University of São Paulo. The study was approved by the local Ethics Committee, and informed consent was obtained before eligibility confirmation. Eligible subjects were adults (18-75 years) with body mass index (BMI) between 25 and 40 kg/m^2 and with prediabetes and normo- or mild-to-moderate hypercholesterolemia.

Prediabetes was defined by the presence of impaired glucose tolerance or impaired fasting glucose according to the World Health Organization. The LDL-C levels were to be less than 200 mg/dL; and triglycerides, less than 300 mg/dL. Exclusion criteria were heart, liver, or kidney diseases; recent weight changes; untreated hypothyroidism; inflammatory illness; myopathy; previous adverse reactions to statins or ezetimibe; and the use of anti-inflammatory drugs or other medications affecting glucose or lipid metabolisms. Blood pressure was to be stable.

During a 2-week run-in period, all participants received dietary counseling and were advised to participate in physical activities. In an open-label manner, 50 subjects were randomly allocated to 2 treatment groups. One group began monotherapy with ezetimibe 10 mg/d (ezetimibe group); and the other, with simvastatin 20 mg/d (simvastatin group), both therapies being maintained for 12 weeks. After completing the monotherapies, both groups received a combination of the drugs for an additional 12-week period. A research assistant counted the pills at the end of each study period to monitor compliance. Treatment was to be discontinued if transaminases rose 3 times higher than the upper limit of reference or 10 times the creatine phosphokinase (CPK). No patient met these criteria. One subject of the ezetimibe group was lost to follow-up because of noncompliance.

Anthropometric measurements were taken during monthly visits. Blood samples were drawn in the morning, after a 12-hour fast, at baseline, and at 12 and 24 weeks of follow-up. Subjects also underwent a 75-g oral glucose tolerance test; fasting and 1- and 2-hour post–glucose load blood samples were obtained to determine plasma glucose and insulin levels. In addition to lipid profile, glucose metabolism was assessed by homeostasis model assessment of insulin resistance (HOMA-IR), area under the curve (AUC) of insulin, and adiponectin levels. The HOMA-IR and AUC provided complementary information on the assessment of insulin sensitivity; increased HOMA-IR indicated hepatic insulin resistance, whereas the AUC of insulin translated into total insulin resistance [36]. Intravascular cellular adhesion molecule–1, E-selectin, PAI-1, and UAE were used as indicative of endothelial function.

2.1. Laboratory analysis

All blood samples were processed in a single laboratory of the Medical School Hospital of the Federal University of Sao Paulo. Plasma glucose, transaminases, CPK, and creatinine were determined by routine methods. Lipid levels (total cholesterol, high-density lipoprotein cholesterol [HDL-C], and triglycerides) were assayed using standard enzymatic methods (Roche Diagnostics, Mannheim, Germany); and LDL-C was calculated using the Friedewald equation. Apolipoprotein B was measured by immunoturbidimetry (Olympus Life and Material Science Europa, Lismeeham, Ireland). Blood samples were stored at −20°C until determination of insulin, adiponectin, PAI-1, ICAM-1, and E-selectin. Urinary albumin excretion was determined from an overnight urine specimen by immunoturbidimetry (Dade Behring, Marburg,Germany). Insulin was analyzed by chemiluminescent immunometric assay (Immulite–Euro/DPC, Llanberis, Gwynedd, United Kingdom), with sensitivity of 2 μIU/mL, intraassay coefficient of variation (CV)

Table 1
Baseline characteristics of the participants according to the initial therapy

	Ezetimibe group	Simvastatin group	*P*
Age (y)	53.4 ± 9.3	53.1 ± 8.1	.893
Sex (F/M)	19/5	19/6	.791
Current smoker	1	3	.609
BMI (kg/m^2)	33.1 ± 4.5	31.9 ± 3.4	.333
Systolic blood pressure (mm Hg)	129.3 ± 16.2	124.0 ± 20.4	.325
Diastolic blood pressure (mm Hg)	83.3 ± 8.7	81.6 ± 11.5	.575
Fasting plasma glucose (mg/dL)	104.3 ± 6.7	110.0 ± 11.7	.041
2-h plasma glucose (mg/dL)	182.3 ± 39.7	175.8 ± 43.4	.586
Fasting insulin (μIU/mL)	11.6 ± 5.3	11.4 ± 5.4	.858
Total cholesterol (mg/dL)	237.4 ± 43.2	214.4 ± 39.7	.058
LDL-C (mg/dL)	145.9 ± 39.9	129.4 ± 36.8	.139
HDL-C (mg/dL)	56.1 ± 13.7	53.1 ± 11.5	.408
Triglycerides (mg/dL)	176.8 ± 85.4	160.0 ± 65.5	.443
AST (U/L)	23.8 ± 10.3	20.9 ± 6.0	.230
ALT (U/L)	26.9 ± 21.0	23.8 ± 9.2	.497
CPK (U/L)	167.9 ± 186.6	135.2 ± 72.8	.421

Data are expressed in number of subjects or mean ± standard deviation. AST indicates aspartate aminotransferase; ALT, alanine aminotransferase.

of 5.2% to 6.4%, and interassay CV of 5.9% to 8.0%. Adiponectin was measured by ELISA, with sensitivity of 0.78 ng/mL, intraassay CV of 7.4%, and interassay CV of 2.4% to 8.4%. Lincoplex kit for human cardiovascular disease (LINCO Research, St Charles, MO) was used to determine ICAM-1 (sensitivity of 9.0 pg/mL, intraassay CV of 7.9%, and interassay CV of 9.7%), E-selectin (sensitivity of 79.0 pg/mL, intraassay CV of 11.2%, and interassay CV of 13.4%), and PAI-1 (sensitivity of 1.0 pg/mL, intraassay CV of 11.8%, and interassay CV of 12.5%).

2.2. Statistical analysis

Data are expressed as mean ± standard deviation or standard error. Unpaired *t* tests were used to compare groups at baseline; and χ^2 analyses, to assess differences in distribution between the treatment groups. Repeated-measures analysis of variance was used to detect differences in clinical and laboratory data across time points and between groups. Pairwise contrasts were made by comparing least-square mean estimates, and *P* values were adjusted for multiple comparisons using the Bonferroni-Holm method. The level of significance was set at .05. Correlation between variables was examined by the Pearson coefficient, and 95% confidence intervals were obtained. Data analysis was performed using Statistical Analysis System (SAS, Chicago, IL) software, version 8.2.

3. Results

Baseline characteristics of the 2 groups of participants who started the protocol with simvastatin or ezetimibe monotherapy were comparable, except for the lower mean fasting plasma glucose values in the ezetimibe group (Table 1). In both groups, their fasting plasma glucose levels remained stable throughout the entire study (24 weeks), as did the magnitude of the difference between them. Antihypertensive regimens and mean values of systolic and diastolic blood pressure did not change during the treatment periods for either group.

The effects of ezetimibe and simvastatin monotherapies and of the combination of drugs on clinical and laboratory parameters are shown in Table 2. Significant decreases in BMI and abdominal circumference were only observed

Table 2
Effects of ezetimibe and simvastatin monotherapies and their combination on clinical and laboratory parameters of subjects in different moments of the study protocol

	Ezetimibe				Simvastatin			
	Baseline	Monotherapy	Combination	*P* value	Baseline	Monotherapy	Combination	*P* value
BMI (kg/m^2)	33.0 ± 0.9	32.4 ± 0.9*	32.4 ± 1.0*	.002	31.9 ± 0.7	31.8 ± 0.7	31.6 ± 0.8	.660
Abdominal circumference (cm)	102.9 ± 2.1	100.6 ± 2.2*	101.4 ± 2.2*	.010	101.8 ± 1.6	101.8 ± 1.6	101.3 ± 1.9	.999
Total cholesterol (mg/dL)	237.4 ± 8.8	197.0 ± 7.2*,†	147.8 ± 6.4‡	<.001	214.4 ± 7.9	165.1 ± 7.3*,†	139.5 ± 7.0‡	<.001
LDL-C (mg/dL)	145.9 ± 8.2	112.5 ± 6.4*,†	66.6 ± 4.8*,‡	<.001	129.4 ± 7.4	81.8 ± 6.2*,†	62.4 ± 5.5*,‡	<.001
HDL-C (mg/dL)	56.1 ± 2.8	55.4 ± 2.1	56.9 ± 2.5	.855	53.1 ± 2.3	53.2 ± 2.4	54.5 ± 2.5	.885
Apolipoprotein B (mg/dL)	115.6 ± 5.0	93.3 ± 4.6*,†	66.9 ± 3.7*,‡	<.001	103.8 ± 4.8	77.9 ± 4.5*,†	63.3 ± 4.0*,‡	<.001
Triglycerides (mg/dL)	176.8 ± 17.4	145.4 ± 15.9*	121.4 ± 11.3*	<.001	160.0 ± 13.1	150.5 ± 17.3	112.6 ± 9.7*,‡	<.001
HOMA-IR	3.0 ± 0.3	2.9 ± 0.3	3.0 ± 0.4	.595	3.1 ± 0.3	3.6 ± 0.4	3.6 ± 0.4	.066
AUC of insulin	9114 ± 1051	8190 ± 992	8901 ± 1060	.151	7554 ± 1013	8611 ± 1.193	8488 ± 1224	.276
Adiponectin (ng/mL)	18.3 ± 1.2	18.6 ± 1.4	17.7 ± 1.9	.731	19.3 ± 1.8	19.5 ± 2.0	20.6 ± 2.8	.645
ICAM-1 (ng/mL)	309.0 ± 35.0	363.2 ± 57.1*,†	302.7 ± 37.1‡	.014	258.0 ± 18.2	242.7 ± 13.9†	259.7 ± 17.1	.781
E-selectin (ng/mL)	43.9 ± 3.5	48.5 ± 4.5*	40.6 ± 3.5‡	.011	44.1 ± 4.1	39.5 ± 2.7	41.9 ± 3.1	.305
PAI-1 (ng/mL)	62.3 ± 3.8	69.5 ± 5.3†	62.6 ± 0.4	.192	55.6 ± 4.8	51.0 ± 3.1†	58.2 ± 4.7	.201
UAE (μg/min)	15.0 ± 6.0	13.2 ± 4.8†	10.0 ± 2.0†	.466	7.4 ± 1.6	4.8 ± 0.7†	4.4 ± 0.9†	.530

Data are expressed by mean ± standard error.

* $P \leq .05$ vs baseline.

† $P \leq .05$ between groups.

‡ $P < .05$ vs week 12.

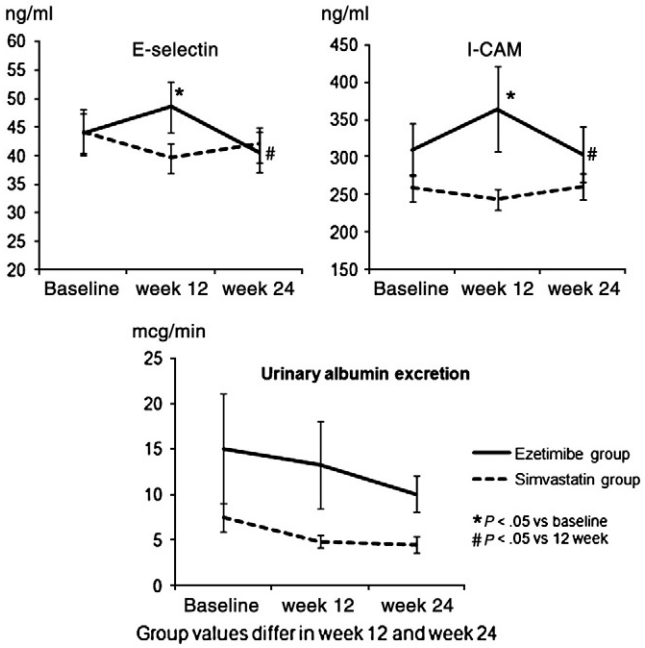

Fig. 1. Mean values of circulating E-selectin and ICAM-1 and UAE in subjects in different moments of the study protocol.

during ezetimibe monotherapy, with no subsequent change during the combined drug therapy. As expected, significant improvements in lipid profile were found after all the therapies. No variation in HOMA-IR, AUC of insulin, and adiponectin levels was observed during the entire study period for either group.

Simvastatin in isolation did not induce changes in E-selectin or ICAM-1 levels, whereas ezetimibe monotherapy increased both variables significantly (Table 2). Only when simvastatin was added to ezetimibe were significant decreases in E-selectin and ICAM-1 observed (Fig. 1), independently of LDL-C changes. As far as PAI-1 and UAE values are concerned, variations within each group were not significant. However, a comparison between groups showed that, at 12 weeks of monotherapy, PAI-1 levels were lower in the simvastatin than in the ezetimibe group (51.0 ± 3.1 vs 69.5 ± 5.3 ng/mL, $P = .005$). A similar pattern was observed regarding UAE values (Fig. 1) because values in the simvastatin group tended to be lower at 12 weeks (4.8 ± 0.7 vs 13.2 ± 4.8, $P = .05$) and 24 weeks (4.4 ± 0.9 vs 10.0 ± 2.0, $P = .02$) than those in the ezetimibe group.

4. Discussion

Our study reinforces observations that simvastatin and ezetimibe are beneficial in lowering total cholesterol, LDL-C, apolipoprotein B, and triglyceride concentrations in subjects at high cardiometabolic risk. We tested whether lipid-lowering agents could also improve insulin sensitivity and endothelial function because such effects could protect against diabetes and atherosclerosis. In accordance with some investigators, no change in putative indicators of insulin sensitivity (HOMA-IR, AUC of insulin, and adiponectin) was found in our study [3,12-14,17].

Most of the clinical trials that have assessed the effect of different statins, at different doses, on glucose metabolism revealed beneficial or neutral results for indices of insulin sensitivity [6-14]. Particularly with regard to therapy with atorvastatin and simvastatin, inconsistent results have been reported, ranging from deleterious to favorable effects [6,7,9,10,13-15]. When looking at combined therapy, Dagli et al [11] showed that a 6-month combination of a low dose of pravastatin (10 mg/d) with ezetimibe daily was associated with a greater improvement in HOMA-IR than isolated pravastatin in higher doses (40 mg/d). The effects of statins on adiponectin levels have been less investigated, and available data are controversial [3,14,15,17,18]. In a previous study, our group found no change in HOMA-IR or adiponectin levels after a 16-week simvastatin treatment [13]. Shorter studies, both in monotherapy or in combination with ezetimibe, also failed to show modifications in adiponectin levels [3,14,17]. However, whereas atorvastatin therapy for 12 weeks induced an increase of adiponectin concentrations in a dose-dependent manner [18], in another study, simvastatin in all doses used (10-80 mg/d) for 8 weeks decreased adiponectin levels [15].

As far as endothelial biomarkers are concerned, our study suggests that simvastatin in isolation may block the deterioration of endothelial dysfunction, which is compatible with the reduction of ICAM-1 and E-selectin observed when simvastatin was added to ezetimibe monotherapy. Several circulating factors produced by the endothelium have been associated with cardiovascular risk [37], although their ability to predict events requires confirmation in prospective studies. Available data regarding the effects of statins on endothelial markers are heterogeneous in terms of population studied, sample size, duration of follow-up, and statin type and doses [23-25,28-33]. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy - Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22), subjects with elevated levels of ICAM-1 had a higher risk of cardiovascular events, which was attenuated by intensive statin therapy [28]. Nevertheless, fluvastatin failed to ameliorate ICAM-1 concentrations in a 3-month treatment study [29]. In a shorter study including diabetic patients, Hogue et al [30] found a reduction in ICAM-1 and E-selectin levels after atorvastatin treatment, 20 mg daily, for 6 weeks. In contrast, Meredith et al [24] showed no difference in E-selectin levels with pravastatin after acute coronary events. As far as we know, no study with a combination of statin and ezetimibe on these parameters is available.

The increases in ICAM-1 and E-selectin values observed after ezetimibe monotherapy may also suggest that ezetimibe could have a deleterious effect on endothelial function. This finding raises questions about the benefits of ezetimibe on atherosclerosis. The main study that has investigated a potential role of the addition of ezetimibe to statin therapy in

atherosclerotic disease—the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial [38], conducted in patients with familial hypercholesterolemia—did not show additional benefits of the combination in changing the intima-media thickness, as compared with simvastatin alone, despite greater decreases in levels of LDL-C and C-reactive protein. Therefore, we cannot exclude a possible adverse effect of ezetimibe on endothelial function favoring the atherosclerotic process.

Elevated levels of PAI-1 are related to increased risk of atherothrombosis [22]; and more recently, its role in predicting incident diabetes has been proposed [39,40]. Particularly for the subset of patients followed in the present study, reduction of this hemostatic marker should be beneficial in diminishing their cardiometabolic risk. Benefits of simvastatin on atherosclerosis are suggested by our finding of lower PAI-1 levels after simvastatin use. Beneficial effects of statins in reducing PAI-1 levels and improving coagulation have been previously proposed despite controversies [33-35]. Laumen et al [33] found that rosuvastatin inhibits PAI-1 expression and release from human adipocytes. Conversely, in the Anti-Inflammatory Effects of Pioglitazone and/or Simvastatin in High Cardiovascular Risk Patients With Elevated High Sensitivity C-Reactive Protein (the PIOSTAT Study), simvastatin failed to reduce PAI-1 levels in high–cardiovascular-risk patients [34]. Otherwise, Nishino et al [35] described an association between higher PAI-1 levels and the presence of thrombus in stent tissue, also observing that preprocedural statins, associated with lower levels of PAI-1, can reduce the thrombotic reaction after stent implantation.

Considering that UAE had been associated with impaired vascular reactivity and with increases in cardiovascular mortality [41], in this study, microalbuminuria was interpreted as an indirect marker of endothelial dysfunction. As far as we know, data on the effect of the statin-ezetimibe combination on UAE are lacking. Despite similar baseline values of UAE, the differences between the groups studied were amplified by simvastatin when compared with the ezetimibe group, without reaching statistical significance. This finding suggests that simvastatin could slow down the atherosclerotic process in the long term. Our data are in agreement with those of several investigators who have described the benefits of statin therapy on albuminuria, mainly in macroalbuminuric patients [25].

Our study has limitations. It was conducted on patients with prediabetes and normo- to moderate hypercholesterolemia, and we cannot generalize our findings to other subsets of subjects. Moreover, the absence of a control group may limit conclusions about the effects of the monotherapies. Some negative results could be dependent on the low statin dose used, short follow-up, and/or small number of subjects included in the study.

In summary, our findings on circulating levels of ICAM-1, E-selectin, and PAI-1 support observations that simvastatin, but not ezetimibe, may be beneficial in preserving endothelial function in prediabetic subjects with normo- or mild-to-moderate hypercholesterolemia. Alternatively, a deleterious effect of ezetimibe on endothelial function is suggested. Simvastatin and ezetimibe, in isolation or combination, do not interfere with insulin resistance. Further studies including bigger study samples and longer follow-up periods are needed to verify these pleiotropic effects of statins, which could be useful in attenuating the cardiometabolic risk of prediabetes.

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