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Lymphocyte-suppressing effect of simvastatin in mixed dyslipidemic patients but not impaired glucose tolerance patients

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Abstract:
This study compared the effect of simvastatin on lymphocyte secretory function between patients with impaired glucose tolerance (IGT) (n = 30) and mixed dyslipidemia (n = 29). Lipid profile, glucose metabolism markers (fasting and 2-h post-glucose challenge glucose levels, HOMA-IR and glycated hemoglobin), plasma CRP levels and the release of interleukin-2 and interferon-γ by phytohemagglutinin-stimulated T lymphocytes were determined before and after 30 and 90 days of simvastatin administration (20 mg daily). Phytohemagglutinin-stimulated T cells from both IGT and mixed dyslipidemic subjects released significantly higher amounts of both cytokines than lymphocytes of 30 dyslipidemia-free individuals with normal glucose tolerance. Despite improving the lipid profile, simvastatin produced no effects on glucose metabolism markers in either treatment groups. The drug normalized the lymphocyte cytokine release and plasma hsCRP in mixed dyslipidemic patients but not in IGT patients. Our study indicates that the presence of mixed dyslipidemia and IGT is associated with the enhanced secretory function of human lymphocytes. Simvastatin is an effective lymphocyte-suppressing agent in mixed dyslipidemic patients but not in IGT patients.

Key words:
simvastatin, mixed dyslipidemia, impaired glucose tolerance, lymphocytes, interleukin-2, interferon-γ

Abbreviations: CRP – C-reactive protein, HbA_{1c} – glycated hemoglobin, HDL – high-density lipoprotein, HMG-CoA – 3-hydroxy-3-methyl-glutaryl-CoA, HOMA-IR index – HOMA insulin resistance index, hsCRP – high sensitivity C-reactive protein, IFG – impaired fasting glucose, IGT – impaired glucose tolerance, LDL – low-density lipoprotein, OGTT – oral glucose tolerance test

Introduction

In addition to improving the lipid profile, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins) produce many extra-lipid effects, including anti-inflammatory and anti-oxidative actions, vasodilatation, an inhibitory action on migration and proliferation of smooth muscle cells, as well as favorable effects on hemostasis and adipose tissue function [1, 2, 6, 7]. These lipid-independent effects may explain the benefits of statin therapy observed in normolipidemic patients with elevated high-sensitivity C-reactive protein (hsCRP) levels [16]. T cells also seem to be a potentially important target for the action of statins. There are a variety of drugs that were found to reduce lymphocyte cytokine release [10, 12] and the expression of activation-induced adhesion mole-

cules on T cells [11], downregulate chemokine receptors on both B and T cells [11], modify the T helper 1/T helper 2 cytokine balance [11] and inhibit clustering of dendritic cells with T cells [25]. Moreover, statins decreased the ability of dendritic cells to induce T cell proliferation [25], reduced the proliferative response of alloreactive T cells to the F344 alloantigen in rats with cardiac transplants [4] and inhibited the proliferation of T cells in response to the interferon-γ-induced expression of MHC class II antigens in different types of cells (primary human endothelial cells, monocytes/macrophages, smooth muscle cells, fibroblasts and some established cell lines) [8, 9, 18]. These multi-directional effects of statins on T cells were found in animals, cell cultures, healthy individuals and subjects with isolated hypercholesterolemia. It remains unknown whether a similar effect is produced in patients with prediabetes. The term 'prediabetes' encompasses impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), two early glucose metabolism abnormalities with relative involvement of insulin secretory defects and hepatic and peripheral insulin resistance [14, 21]. Both of these prediabetic states, particularly IGT, are associated with an increased risk of the development of overt diabetes and cardiovascular diseases [14, 21].

To the best of our knowledge, the effects of HMG-CoA reductase inhibitors on lymphocyte function in mixed dyslipidemic and prediabetic patients have never been a subject of clinical research. Therefore, we decided to determine the action of simvastatin on the lymphocyte release of interleukin-2 and interferon-γ, relating the strength of this action to the metabolic status of subjects. Moreover, we investigated whether the potential lymphocyte-suppressing effect of simvastatin contributes to its anti-inflammatory action.

Materials and Methods

Patients

Patients were considered eligible for enrollment if they had (1) newly diagnosed and previously untreated primary mixed dyslipidemia (plasma total cholesterol > 200 mg/dl, LDL-cholesterol > 130 mg/dl, triglycerides > 150 mg/dl) or isolated IGT (fasting plasma glucose < 100 mg/dl and 2-h post-challenge glucose ≥ 140 mg/dl (7.78 mmol/l) and < 200 mg/dl (11.1 mmol/l)), and (2) asymptomatic atherosclerosis (common carotid intima-media thickness ≥ 0.7 mm). All subjects (35 with mixed dyslipidemia and 37 with IGT) were instructed to follow the Therapeutic Lifestyle Changes diet. After 90 days of lifestyle modification, we repeated the 75 g oral glucose tolerance test (OGTT) and the lipid profiling, and 59 patients who still fulfilled the criteria of the initial diagnosis were included. Mixed dyslipidemic (n = 30) and IGT (n = 29) patients were compared with 30 age-, sex- and weight-matched subjects with asymptomatic atherosclerosis and no lipid and glucose metabolism abnormalities. The study was performed in accordance with the 1964 Helsinki Declaration. All patients provided written, informed consent. The study protocol was approved by the local ethical committee.

The exclusion criteria included (1) age < 25 or > 70 years; (2) concomitant presence of mixed dyslipidemia and IGT; (3) isolated primary hypercholesterolemia or hypertriglyceridemia; (4) secondary dyslipidemia; (5) diabetes mellitus or IFG; (6) acute and chronic inflammatory processes; (7) symptomatic congestive heart failure; (8) unstable angina, myocardial infarction or stroke within 6 months preceding the study; (9) arterial hypertension (ESC/ESH grade 2 or 3); (10) impaired renal or hepatic function; (11) malignancy within 5 years preceding the study; (12) treatment with other hypolipemic agents within 3 months prior to the study; (13) treatment with other drugs known to either affect plasma glucose or lipid levels or to interact with statins; (14) treatment with drugs that may affect inflammation; (15) hormonal replacement therapy or oral contraception; and (16) poor patient's compliance.

All enrolled patients were treated for 90 days with simvastatin (20 mg daily), administered once daily at bedtime without any changes in dosage during the entire study period. The investigation of possible simvastatin-induced side effects was performed fortnightly. Overt myopathy and elevated levels of aminotransferases (> 3 times above the normal limit) and creatine kinase (> 10 times above the normal limit) were considered an indication for withdrawal of treatment. Compliance was determined during each visit by the number of tablets returned and was regarded as satisfactory if the percentage of tablets taken by a patient ranged from 90% to 110%.

Laboratory assays

Laboratory assays (plasma lipids, OGTT, insulin, glycated hemoglobin (HbA_{1c}), hsCRP and lymphocyte cytokine secretion) were carried out at baseline and after 30 and 90 days of simvastatin administration. Venous blood samples were taken 12 h after the last meal. To minimize analytical errors, all assays were performed in duplicate within 48 h after sample collection by a person blinded to the patient identity and study protocol. Lipid profiles and plasma glucose were assayed by routine laboratory techniques (bioMerieux, Marcy l'Etoile, France; Beckman, Palo Alto, CA, USA). LDL levels were measured directly. Plasma insulin was measured with a commercial radioimmunoassay kit (Linco Research Inc., St. Charles, MO, USA). The HOMA insulin resistance index (HOMA-IR) was calculated using the following formula: HOMA-IR = fasting glucose (mg/dl) × fasting insulin (μU/ml)/405 [22]. HbA_{1c} was determined using a commercially available kit obtained from Sigma (St. Louis, MO, USA). Plasma levels of CRP were measured using a high-sensitivity monoclonal antibody assay (MP Biomedicals, Orangeburg, NY, USA). Phytohemagglutinin-treated cultures of human T lymphocytes were performed as described previously [12]. Cytokine (interleukin-2 and interferon-γ) release was determined with the use of commercial ELISA kits (R&D Systems, McKinley Place N.E. Minneapolis, MN, USA), according to the manufacturer's instructions. The minimum detectable levels were 8 pg/ml for interleukin-2 and 15 pg/ml for interferon-γ.

Statistical analyses

Comparisons between the groups were performed using one-way ANOVA followed by the *post-hoc* Bonferroni test (lipid profile, pre- and post-OGTT plasma glucose, HbA_{1c}) or the Kruskal-Wallis test followed by the Mann-Whitney U test (HOMA-IR, interleukin-2 and interferon-γ). To compare pre-, inter- and post-therapy data within the same treatment group, the Student's paired *t* test (lipid profile, plasma glucose and HbA_{1c}) or the Wilcoxon test (HOMA-IR, hsCRP and cytokines) were applied. Correlations between metabolic variables and the markers of inflammation were

Tab. 1. Baseline characteristics of participants

	Controls	Impaired glucose tolerance	Mixed dyslipidemia
Number of patients	30	30	29
Age (years)	50.4 ± 2.4	52.0 ± 3.2	51.4 ± 4.7
Women/men	12/18	13/17	11/18
Body mass index (kg/m^2)	27.2 ± 2.0	26.9 ± 2.5	28.0 ± 1.4
Smokers (%)	36.7	33.3	34.5
Intima-media thickness (mm)	0.86 ± 0.06	0.88 ± 0.05	0.89 ± 0.06 $^{\$\$\$}$
Total cholesterol (mg/dl)	172.4 ± 6.4 (4.46 ± 0.17)	173.0 ± 6.8 (4.47 ± 0.18)	248.8 ± 10.1 (6.43 ± 0.26)*** $^{\$\$\$}$
LDL cholesterol (mg/dl)	96.8 ± 5.0 (2.50 ± 0.13)	95.2 ± 4.8 (2.46 ± 0.12)	155.0 ± 8.7 (4.01 ± 0.22)***
HDL cholesterol (mg/dl)	51.8 ± 1.5 (1.34 ± 0.04)	52.1 ± 2.0 (1.35 ± 0.05)	47.1 ± 3.1 (1.22 ± 0.08) $^{\$\$\$}$
Triglycerides (mg/dl)	119.8 ± 7.4 (1.37 ± 0.08)	124.2 ± 8.5 (1.42 ± 0.10)	225.1 ± 15.2 (2.57 ± 0.17)***
Fasting glucose (mg/dl)	84.1 ± 2.2 (4.67 ± 0.12)	88.0 ± 4.1 (4.89 ± 0.23) $^{\#\#\#}$	86.1 ± 2.5 (4.78 ± 0.14)
2-h post-glucose load plasma glucose (mg/dl)	118.1 ± 5.1 (6.56 ± 0.28)	170.1 ± 7.1 (9.45 ± 0.39)*** $^{\#\#\#}$	119.8 ± 4.1 (6.65 ± 0.23)
HbA_{1c} (%)	4.7 ± 0.2	6.1 ± 0.3*** $^{\#\#\#}$	4.8 ± 0.3
HOMA-IR index	2.2 ± 0.1	5.7 ± 0.4***	2.5 ± 0.3
hsCRP (mg/l)	1.1 ± 0.2	3.8 ± 0.4***	3.9 ± 0.4***
Interleukin-2 release (ng/ml)	3.0 ± 0.3	5.9 ± 0.3***	6.0 ± 0.4***
Interferon-γ release (ng/ml)	31.6 ± 3.8	66.4 ± 7.1***	64.2 ± 5.9***

Data represent the mean ± SD. Numbers in parentheses represent values in mmol/l. *** $p < 0.001$ *vs.* control group. $^{\#\#}$ $p < 0.01$, $^{\#\#\#}$ $p < 0.001$ *vs.* patients with mixed dyslipidemia. $^{\$\$\$}$ $p < 0.001$ *vs.* patients with impaired glucose tolerance

assessed using Kendall's tau test. Statistical analysis was carried out by means of the GraphPad Prism 2.01 software (GPA-26576-117) and Statistica 6.1 (axxp-308a903804ar).

Results

Baseline characteristics of patients

No significant differences were observed in the age, sex, weight and medical backgrounds between the groups at the onset of the study (Tab. 1). Mixed dyslipidemic subjects had higher total cholesterol, LDL-cholesterol and triglyceride levels and lower levels of HDL-cholesterol than IGT and control subjects. Compared to the remaining groups, IGT individuals exhibited increased 2-h post-glucose load plasma glucose, HbA_{1c}, and the HOMA-IR index. Interleukin-2 and interferon-γ release by phytohemagglutinin-induced T cells as well as plasma hsCRP levels were higher in mixed dyslipidemic and IGT patients compared with the control subjects, with no differences observed between the two groups.

Control group

Plasma lipids, fasting glucose and 2-h post-glucose load plasma glucose, HbA_{1c}, the HOMA-IR index, plasma hsCRP and lymphocyte cytokine release all remained at similar levels during the entire study period (Tab. 2).

Simvastatin-treated individuals

Lipid profile and glucose metabolism

Simvastatin treatment of IGT and mixed dyslipidemic subjects resulted in a decrease of total and LDL cholesterol (Tab. 2). Moreover, simvastatin reduced the level of triglycerides and increased HDL-cholesterol in mixed dyslipidemic patients but not in IGT patients. The drug did not affect fasting and 2-h post-glucose load plasma glucose, HbA_{1c} or the HOMA-IR.

Systemic inflammation and lymphocyte cytokine release

Simvastatin administered to mixed dyslipidemic subjects reduced plasma hsCRP by 28.2% ($p < 0.01$) and 61.5% ($p < 0.001$), interleukin-2 release by 20.0% ($p < 0.05$) and 48.3% ($p < 0.001$), and interferon-γ release by 24.3% ($p < 0.01$) and 53.1% ($p < 0.001$) after 30 and 90 days of treatment, respectively. The effect of simvastatin on these variables was time-dependent. Post-treatment values of the assessed markers did not differ from those observed in the control group. Neither 30- nor 90-day treatment with simvastatin significantly changed plasma hsCRP levels or lymphocyte cytokine release in IGT patients.

Correlations

At the onset of the study, plasma hsCRP levels were correlated with lymphocyte release of interleukin-2 (mixed dyslipidemic subjects: $r = 0.57$, $p < 0.001$; IGT patients: $r = 0.53$, $p < 0.001$) and interferon-γ (mixed dyslipidemic subjects: $r = 0.60$, $p < 0.001$; IGT patients: $r = 0.55$, $p < 0.001$). In mixed dyslipidemic individuals, the action of simvastatin on hsCRP was correlated with simvastatin-induced changes in interleukin-2 ($r = 0.53$, $p < 0.001$) and interferon-γ ($r = 0.56$, $p < 0.001$) release. There was no correlation between metabolic variables (plasma lipids, glucose metabolism markers) and hsCRP or lymphocyte cytokine release at entry, during or after simvastatin treatment.

Adverse effects

No significant adverse effects were observed during the entire study period. All patients complied with the study protocol and completed the study.

Discussion

Our study has revealed that lymphocyte secretion of interleukin-2 and interferon-γ was increased to a similar degree in both mixed dyslipidemic and IGT patients. The finding that the presence of both these disorders was accompanied by abnormal cytokine release may partially explain the enhanced risk of vascular disorders in IGT and mixed dyslipidemic subjects, as interleukin-2 and interferon-γ are considered

Tab. 2. The effect of simvastatin on the lipid profile, glucose metabolism markers, hCRP and lymphocyte cytokine release according to metabolic status

	Control subjects	Impaired glucose tolerance	Mixed dyslipidemia
Total cholesterol (mg/dl)			
Baseline	172.4 ± 6.4 (4.46 ± 0.17)	173.0 ± 6.8 (4.47 ± 0.18)$^{\$}$	248.8 ± 10.1 (6.43 ± 0.26)$^{\#\#\#***\$\$\$}$
After 30 days	169.1 ± 6.5 (4.37 ± 0.17)	135.1 ± 6.2 (3.49 ± 0.16)$^{\&\&\&*}$	200.2 ± 8.2 (5.18 ± 0.21)$^{\&\&\&\$\$**}$
After 90 days	168.7 ± 6.8 (4.36 ± 0.18)	132.2 ± 4.7 (3.42 ± 0.12) *	192.4 ± .1 (4.98 ± 0.13) *
LDL cholesterol (mg/dl)			
Baseline	96.8 ± 5.0 (2.50 ± 0.13)	95.2 ± 4.8 (2.46 ± 0.12)$^{\&\&\&}$	155.0 ± 8.7 (4.01 ± 0.22)$^{\#\#\#***\$\$\$}$
After 30 days	94.6 ± 5.5 (2.45 ± 0.14)	64.2 ± 6.2 (1.66 ± 0.16)$^{\&\&\&***}$	110.2 ± 8.6 (2.85 ± 0.22)$^{\&\&\&*\$\$\$}$
After 90 days	94.2 ± 5.6 (2.43 ± 0.14)	63.2 ± 5.3 (1.63 ± 0.14) ***	106.4 ± 5.1 (2.75 ± 0.13) *
HDL cholesterol (mg/dl)			
Baseline	51.8 ± 1.5 (1.34 ± 0.04)	52.1 ± 2.0 (1.35 ± 0.05)	47.1 ± 3.1 (1.22 ± 0.08)
After 30 days	52.4 ± 2.3 (1.36 ± 0.06)	54.5 ± 2.7 (1.41 ± 0.07)	53.4 ± 2.8 (1.38 ± 0.07)$^{\$}$
After 90 days	52.8 ± 4.0 (1.37 ± 0.10)	56.1 ± 3.1 (1.45 ± 0.08)	54.2 ± 3.2 (1.40 ± 0.08)
Triglycerides (mg/dl)			
Baseline	119.8 ± 7.4 (1.37 ± 0.08)	124.2 ± 8.5 (1.42 ± 0.10)	225.1 ± 15.2 (2.57 ± 0.17)$^{\#\#\#***\$\$\$}$
After 30 days	122.4 ± 8.5 (1.40 ± 0.10)	112.1 ± 8.6 (1.28 ± 0.10)	187.0 ± 9.6 (2.13 ± 0.11)$^{***\$\$\$}$
After 90 days	120.1 ± 5.0 (1.37 ± 0.06)	110.2 ± 7.8 (1.26 ± 0.09)	185.1 ± 10.6 (2.11 ± 0.12) ***
Fasting glucose (mg/dl)			
Baseline	84.1 ± 2.2 (4.67 ± 0.12)	88.0 ± 4.1 (4.89 ± 0.23)	86.1 ± 2.5 (4.78 ± 0.14)
After 30 days	83.4 ± 2.9 (4.63 ± 0.16)	84.9 ± 3.5 (4.72 ± 0.19)	85.0 ± 3.0 (4.72 ± 0.17)
After 90 days	82.9 ± 3.0 (4.61 ± 0.17)	83.6 ± 3.2 (4.64 ± 0.18)	84.7 ± 3.5 (4.71 ± 0.19)
2-h post-glucose load plasma glucose (mg/dl)			
Baseline	118.1 ± 5.1 (6.56 ± 0.28)	170.1 ± 7.1 (9.45 ± 0.39)***^^^	119.8 ± 4.1 (6.65 ± 0.23)
After 30 days	121.0 ± 5.0 (6.72 ± 0.28)	168.0 ± 5.8 (9.33 ± 0.32)***^^^	123.1 ± 4.2 (6.84 ± 0.23)
After 90 days	117.3 ± 4.8 (6.52 ± 0.27)	166.9 ± 8.3 (9.27 ± 0.46)***^^^	123.6 ± 6.7 (6.87 ± 0.37)
HbA_{1c} (%)			
Baseline	4.7 ± 0.2	6.1 ± 0.3***^^	4.8 ± 0.3
After 30 days	4.8 ± 0.2	6.0 ± 0.3***^^	4.8 ± 0.3
After 90 days	4.7 ± 0.2	5.9 ± 0.2***^^	4.9 ± 0.2
HOMA-IR index			
Baseline	2.2 ± 0.1	5.7 ± 0.4***^^^	2.5 ± 0.3
After 30 days	2.0 ± 0.3	5.5 ± 0.4***^^^	2.4 ± 0.2
After 90 days	2.0 ± 0.2	5.3 ± 0.5***^^^	2.3 ± 0.2
hsCRP (mg/l)			
Baseline	1.1 ± 0.2	3.8 ± 0.4***	3.9 ± 0.4$^{\#\#***\$}$
After 30 days	1.3 ± 0.3	3.7 ± 0.3***	2.8 ± 0.3$^{\&\&\&***\$\$\$}$
After 90 days	1.3 ± 0.2	3.5 ± 0.4***	1.5 ± 0.4
Interleukin-2 release (ng/ml)			
Baseline	3.0 ± 0.3	5.9 ± 0.3***	6.0 ± 0.4$^{\#\#***}$
After 30 days	2.8 ± 0.3	5.6 ± 0.4***	4.8 ± 0.4$^{\&\&\&***\$\$\$}$
After 90 days	2.9 ± 0.2	5.7 ± 0.4***	3.1 ± 0.2
Interferon-γ release (ng/ml)			
Baseline	31.6 ± 3.8	66.4 ± 7.1***	64.2 ± 5.9$^{\#\#***\$}$
After 30 days	30.2 ± 3.5	62.5 ± 8.4***	48.6 ± 5.3$^{\&\&\&***\$\$\$}$
After 90 days	29.8 ± 4.1	60.2 ± 6.9***	30.1 ± 4.7

Data represent the mean ± SD. Numbers in parentheses represent values in mmol/l. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs.* control group. $^{\#}$ $p < 0.05$, $^{\#\#}$ $p < 0.01$, $^{\#\#\#}$ $p < 0.001$ *vs.* pretreatment values. $^{\$}$ $p < 0.05$, $^{\$\$\$}$ $p < 0.001$ *vs.* patients with impaired glucose tolerance. $^{\wedge\wedge}$ $p < 0.01$, $^{\wedge\wedge\wedge}$ $p < 0.001$ *vs.* patients with mixed dyslipidemia. $^{\&\&\&}$ $p < 0.001$ *vs.* respective value after 30 days of treatment

cardiovascular risk factors [20]. Because our study included patients with either isolated glucose metabolism abnormalities or isolated lipid profile disturbances, we cannot exclude the fact that the secretory function of the lymphocytes may be even more disturbed if these abnormalities coexist with each other. As T cells are involved in the development and progression of atherosclerosis [23], restoration of their normal secretory function may inhibit this pathological process.

Despite a similar degree of disturbances in lymphocyte secretory function at the baseline, simvastatin reduced interleukin-2 and interferon-γ release only in mixed dyslipidemic subjects. Interestingly, this lymphocyte-suppressing effect was accompanied by a reduction in the plasma level of hCRP, a protein that is considered a key marker of systemic inflammation and that is directly involved in the process of atherogenesis [15]. This finding suggests that cellular pathways underlying abnormal lymphocyte cytokine release in mixed dyslipidemia are more sensitive to statins than those in IGT. Although the effect on lymphocyte cytokine secretion and systemic inflammation does not precisely reflect the global pleiotropic action of simvastatin, our results indicate that mixed dyslipidemic patients may benefit more from simvastatin treatment than IGT subjects. Interestingly, despite reducing monocyte secretory function with a similar potency by atorvastatin and fenofibrate [13], fenofibrate and ciprofibrate only insignificantly reduced interleukin-2 and interferon-γ release by the activated lymphocytes of mixed dyslipidemic subjects [12]. These results suggest the superiority of statin over fibrate therapy in mixed dyslipidemic subjects. Interestingly, the opposite seems to be true for IGT patients. Our recent observations [Krysiak et al., submitted] have shown a clear interleukin-2 and interferon-γ-lowering action of fenofibrate, which contrasts with a lack of simvastatin effect in the present study. The fact that the lymphocyte-suppressing effect of simvastatin in mixed dyslipidemic subjects was higher at the end of the treatment than after 30 days of therapy may serve as an argument for long-term usage of statins by patients with abnormal lipid metabolism.

The effect of simvastatin on the secretory function of human T cells was unrelated to the lipid-improving effects of this agent. This suggests that a reduction in lymphocyte cytokine release in simvastatin-treated mixed dyslipidemic patients is probably secondary to a statin-induced decrease in protein prenylation. The latter process involving the inhibition of the synthesis of non-sterol mevalonate derivatives, such as farnesyl and geranylgeranyl pyrophosphates, is responsible for the regulation of numerous other cellular processes by HMG-CoA reductase [5, 6]. The finding that no effect in lymphocyte cytokine release and plasma hsCRP was observed in IGT patients suggests that enhanced posttranslational protein prenylation plays a greater role in the development of a proinflammatory state in mixed dyslipidemia than in IGT.

Despite some concerns about the potentially deteriorating influence of HMG-CoA reductase inhibitors on insulin secretion and action [17, 19, 24], we have observed a neutral effect of simvastatin on glucose metabolism. These results suggest that simvastatin does not seem to have a negative impact on the natural course of IGT. Moreover, considering the relationship between inflammation and the onset and progression of diabetes [3], simvastatin may even delay the development of diabetes in mixed dyslipidemic individuals.

Our study has at least three limitations. First, the study included a limited number of patients, and therefore, its results should be supported by a larger study. Second, the dose of simvastatin used in our study was relatively small. We cannot exclude the possibility that simvastatin may also affect cytokine release and plasma hsCRP in IGT patients if administered at higher doses. Third, because of the short duration of treatment, the question of whether long-term treatment might more prominently affect lymphocyte secretory function and systemic inflammation in IGT patients remains unresolved.

In summary, our study has shown that the secretory function of T cells is disturbed in mixed dyslipidemic and IGT patients. Despite lowering lipid levels in both treatment groups, simvastatin reduced cytokine release and, consequently, systemic inflammation only in the mixed dyslipidemic subjects. This finding suggests that mixed dyslipidemic patients are better candidates for statins than individuals with IGT.

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