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Pleiotropic effects of pitavastatin: a pilot study using the saphenous vein endothelial cell model of endothelial injury and prevention of atherosclerosis

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Abstract. – OBJECTIVE: Cardiovascular diseases are responsible for the majority of deaths on a global scale. Atherosclerosis is the main risk factor for cardiovascular disorders and represents a complex phenomenon associated with endothelial dysfunction and inflammation. Statins, especially atorvastatin (ATV) and pitavastatin (PTV), are common agents used to control ongoing atherosclerotic events in the body to minimize cardiovascular disease-based deaths.

MATERIALS AND METHODS: The present study aimed at comparing the efficacy of ATV and PTV in a cell line model of inflammation. Human saphenous vein cells were treated with TNF-alpha to mimic atherosclerotic conditions, and the cells were divided into 7 groups, including control, DMSO, TNF-alpha (10 ng/mL-6 hours), ATV (50 μM/24 hours), PTV (2 μM/24 hours), ATV (50 μM/24 hours)+TNF-alpha (10 ng/mL-6 hours) and PTV (2 μM/24 hours)+TNF-alpha (10 ng/mL-6 hours). The expression levels of 20 proinflammatory cytokines and chemokines were investigated in these groups using a human atherosclerosis antibody array.

RESULTS: Possible pathway interactions were determined by STRING and PANTHER analyses. Comparison with the effect of ATV indicated that PTV reduced the levels of 4 proinflammatory cytokines: CCL11, CSF2, CCL20, and TGFB1 ($p<0.05$).

CONCLUSIONS: Pleiotropic effects of pitavastatin against cardiovascular diseases appeared to be better; however, additional studies are required to compare statins and to identify new drugs that maintain broader protection from the risks of cardiovascular diseases.

Key Words:
Cardiovascular diseases, Atherosclerosis, Atorvastatin, Pitavastatin, Inflammation.

Introduction

Cardiovascular diseases (CVDs) are among major causes of death, accounting for one-third of all deaths globally[1]. Atherosclerosis is the most common cause of CVD mortality; it is an inflammatory disorder defined as the changes in lipoprotein metabolism that result in an increase in the levels of pro-inflammatory and pro-oxidant lipids and an immunological response[2]. Atherogenesis is induced by a complex combination of several phases, such as inflammation, accumulation of lipids, smooth muscle cell proliferation, and dysfunction of endothelial cells[3].

Atherosclerosis and a variety of other cardiovascular problems are governed by inflammation and the immune system[4]. Associations between circulating proinflammatory cytokines and future cardiovascular events have been reported in the healthy population and subjects with CVD[5].

Tumor necrosis factor (TNF)-alpha is one of the pro-inflammatory cytokines that play a pivotal role in both the onset and progression of atherosclerotic and regulates several pro-atherosclerotic pathways to stimulate endothelial cells, leading to the expression of adhesion molecules, such as intercellular adhesion molecule-1 and vascular cell adhesion molecules, and of proinflammatory cytokine receptors. These processes initiate the synthesis and release of a wide range of inflammatory cytokines to activated leukocytes that are recruited to an inflammatory lesion[6,7]. The studies on the principles of the pathobiology of atherosclerosis revealed that these changes in endothe-

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lial function may contribute to the formation and progression of atherosclerotic plaques and to the corresponding clinical consequences.

Numerous studies have reported that a reduction in the plasma levels of cholesterol is the cornerstone factor for the minimization of the number of patients suffering from cardiovascular events. Statins block 3-hydroxyl-3-methyl coenzyme A reductase to reduce cholesterol production and vascular inflammation[8,9]. The most significant effect of statin therapy includes the influence of these drugs on plaque composition to increase plaque stability and lower the possibility of plaque rupture[10,11].

Pitavastatin is a new generation statin with a unique chemical structure, minimal drug-drug interactions, and a higher degree of systemic bioavailability; the anti-atherosclerotic effect of this drug involves the suppression of the proliferation of pulmonary artery smooth muscle cells[12-14]. Atorvastatin has an anti-inflammatory effect, in addition to the cholesterol-lowering effect, and is a common statin used to treat hypercholesterolemia and/or atherosclerosis[15,16].

The current study investigated the pleiotropic effects of pitavastatin and compared the efficacy of atorvastatin and pitavastatin in attenuation of inflammation-mediated atherosclerosis in human saphenous vein cells (HSaVECs) in an inflammatory cell culture model induced by TNF-alpha.

Materials and Methods

Cell Culture

Human saphenous vein endothelial cells (HSaVECs; catalog number: PromoCell C-12231) were thawed and cultured according to the supplier's protocol. In brief, 25 cm^2 flasks were coated with type I collagen. A total of $5x10^5$ HSaVECs per flask were cultivated in Promocell endothelial cell growth medium (C-22010). After incubation at 37°C, 5% CO_2 until full confluence, the cells were subcultured into 6-well plates and then treated with the drugs. When the cells cultivated on 6-well plates reached 70-80% confluence, atorvastatin, pitavastatin, and TNF-α were administered. DMSO was used to solve TNF-α and the drugs atorvastatin and pitavastatin.

Drug Administration

Cultured HSaVECs were pretreated with 50 μM atorvastatin (ATV) or 2 μM pitavastatin (PTV) for 24 hours. Then, 10 ng/mL TNF-α were administered for 6 hours to mimic atherosclerotic conditions. The doses and duration of the treatments are presented in Table I.

Human Atherosclerosis Antibody Array

The following proinflammatory cytokines and chemokines were detected in HSaVECs by chemiluminescence-based dot blot method using a RayBio C-Series human atherosclerosis antibody array C1 (code: AAH-ATH-1, Raybiotech, Norcross, GA): eotaxin-1 (CCL11), regulated upon activation normal T cell expressed and presumably secreted (CCL5), macrophage inflammatory protein-3 alpha (CCL20), monocyte chemoattractant protein-1 (CCL2), colony-stimulating factor 3 (CSF3), colony-stimulating factor 2 (CSF2), colony-stimulating factor 1 (CSF1), glial cell-derived neurotrophic factor (GDNF), interferon-gamma (IFNG), intercellular adhesion molecule 1 (ICAM1), interleukin 1 receptor type II (IL1R2), interleukin 1 beta (IL1B), interleukin 1 alpha (IL1A), interleukin 1 receptor type I (IL1R1), tumor necrosis factor-beta (LTA), platelet-derived growth factor-BB (PDGFB), tumor necrosis factor-alpha (TNFA), transforming growth factor-beta 3 (TGFB3), transforming growth factor-beta 2

Table I. The dose and duration of drug administration.

Group	Atorvastatin (ATV) Dose/Duration	Pitavastatin (PTV) Dose/Duration	TNF-alpha Dose/Duration
Control	-	-	-
DMSO	-	-	-
TNF- α	-	-	10 ng/mL (6 hours)
ATV	50 μM (24 hours)	-	-
PTV	-	2 μM (24 hours)	-
ATV+TNF-α	50 μM (24 hours)	-	10 ng/mL (6 hours)
PTV+TNF-α	-	2 μM (24 hours)	10 ng/mL (6 hours)

DMSO: Dimethyl sulfoxide; TNF-α: Tumor necrosis factor-alpha; ATV: Atorvastatin; PTV: Pitavastatin.

Table II. The overall distribution of the antibodies to proinflammatory proteins in the human atherosclerosis antibody dot-blot array.

	A	B	C	D	E	F	G	H
1	Positive Control	Positive Control	Negative Control	Negative Control	Eotaxin-1 (CCL11)	G-CSF	GDNF	GM-CSF (CSF2)
2								
3	ICAM-1	IL-1 R1	IL-1 R2	IFN-Gamma	IL-1 Alpha	IL-1 Beta	MCP-1 (CCL2)	M-CSF
4								
5	MIP-3 Alpha (CCL20)	PDGF-BB	RANTES (CCL5)	TGF Beta 1	TGF Beta 2	TGF Beta 3	TNF Alpha	TNF Beta (LTA)
6								
7	NTC	NTC	NTC	NTC	NTC	NTC	NTC	Positive Control

NTC: Nontemplate control.

(TGFB2), and transforming growth factor-beta 1 (TGFB1). The experiments were repeated 2 times in duplicate. The distribution of the antibodies on a dot blot array is shown in Table II.

Protein Pathway Analysis

Proteins with statistically significant differences in their expression levels between groups were then analyzed for possible coexpression, interactions, and intervening degree. The online tool GeneMANIA[17] was used to identify the biological network status of these proteins. The proteins were also analyzed using another online tool, PANTHER[18], to identify possible pathway associations.

Statistical Analysis

The dot blot expression data were analyzed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics included the median, mean and lowest-highest values. The data distribution was analyzed with Kolmogorov-Smirnov test. Since the tested data were not normally distributed, the data of the study were analyzed by Mann-Whitney U and Kruskal-Wallis' tests. The level of statistical significance was set as $p \leq 0.05$. The expression levels of the proinflammatory cytokines and chemokines in the groups were compared using Dunn's multiple comparisons test.

Results

Human Atherosclerosis Antibody Array

The expression levels of 20 proinflammatory cytokines and chemokines in seven sample groups were evaluated using a dot-blot array (Figure 1). The results of statistical analysis of the expression array revealed significant differences between the groups in the expression of four proinflammatory cytokines, including eotaxin-1 (CCL11), colony-stimulating factor 2 [GMCSF (CSF2)], macrophage inflammatory protein-3 alpha (CCL20) and transforming growth factor-beta 1 (TGFB1).

Increases in the expression levels of CCL11, CSF2, CCL20, and TGFB1 were statistically significant in the TNF-α groups compared to those in the control groups ($p \leq 0.05$). A decrease in CCL11 expression levels was statistically significant in the PTV and TNF-α + PTV groups compared to that in the TNF-α group ($p \leq 0.05$).

In the case of CSF2 levels, a decrease was statistically significant in the ATV ($p \leq 0.05$) and PTV groups ($p \leq 0.001$), compared to the TNF-α group. However, the CSF2 level was increased in the TNF-α + PTV group compared to that in the PTV ($p \leq 0.05$) and control groups ($p \leq 0.01$). In addition, CSF2 levels were higher in the TNF-α + ATV group compared to the control group ($p \leq 0.05$).

A decrease in CCL20 expression levels was statistically significant in the PTV ($p \leq 0.05$) and ATV groups ($p \leq 0.01$), compared to that in the TNF-α group. ATV administration resulted in a lower expression level of CCL20 in the ATV group compared to that in the TNF-α + ATV ($p \leq 0.05$) and TNF-α + PTV ($p \leq 0.001$) groups.

A decrease in TGFB1 expression levels was statistically significant in the PTV group compared to that in the TNF-α group ($p \leq 0.001$) (Figure 2).

There were no statistically significant differences in the expression levels of CCL2, CCL5, CSF1, CSF3, GDNF, ICAM1, IFNG, IL1A, IL1B, IL1R1, IL1R2, LTA, PDGFB, TGFB2, TGFB3, and TNFA.

Protein Pathway Analysis

According to the predictions of biological network analysis, CCL11 and CCL20 physically interacted with the proteins of the similar families, i.e., chemokines and their precursors, such as

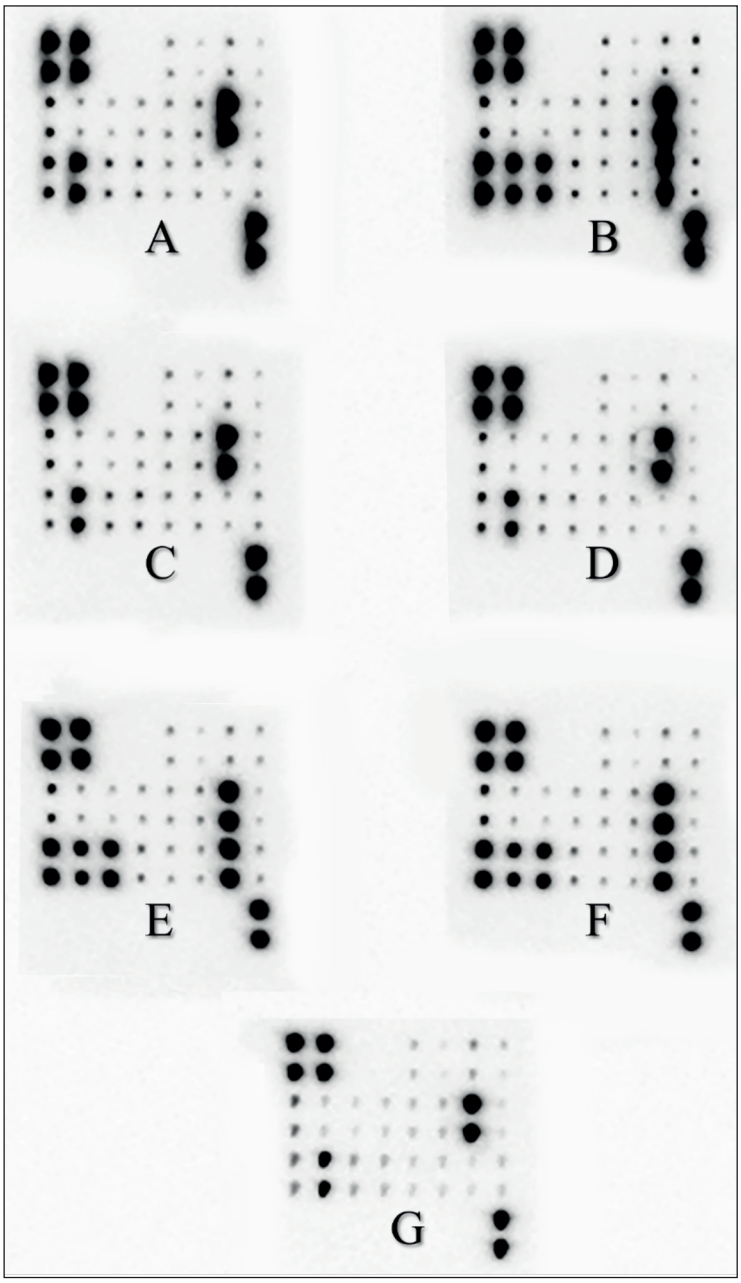

Figure 1. The dot blot arrays of proinflammatory cytokines and chemokines of all groups. **A,** Control group, **B**, TNF-α group (10 ng/mL/6 hours), **C**, ATV group (50 μM/24 hours), **D**, PTV group (2 μM/24 hours), **E**, ATV + TNF-α group, **F**, PTV + TNF-α group and **G,** DMSO alone group.

CXCL3, CXCL5, CXCL12, and CCL18, in cytokine receptor binding, chemokine receptor binding, cytokine activity, leukocyte chemotaxis and cellular response to a chemokine (Figure 3).

In addition, the results of biological process analysis by the PANTHER online tool indicated that all 4 identified proteins (CCL11, CCL20, GMCSF, and TGFB1) had a function in the cellular processes. Three out of 4 proteins were responsible for biological regulation, immune system processes, and response to stimulus and signaling. Two out of 4 proteins functions in the biological processes were involved in interspecies interactions between organisms, localization, and locomotion. In addition, one out of these 4 proteins was related to the following processes: developmental process, metabolic process, and multicellular organismal process (Figure 4).

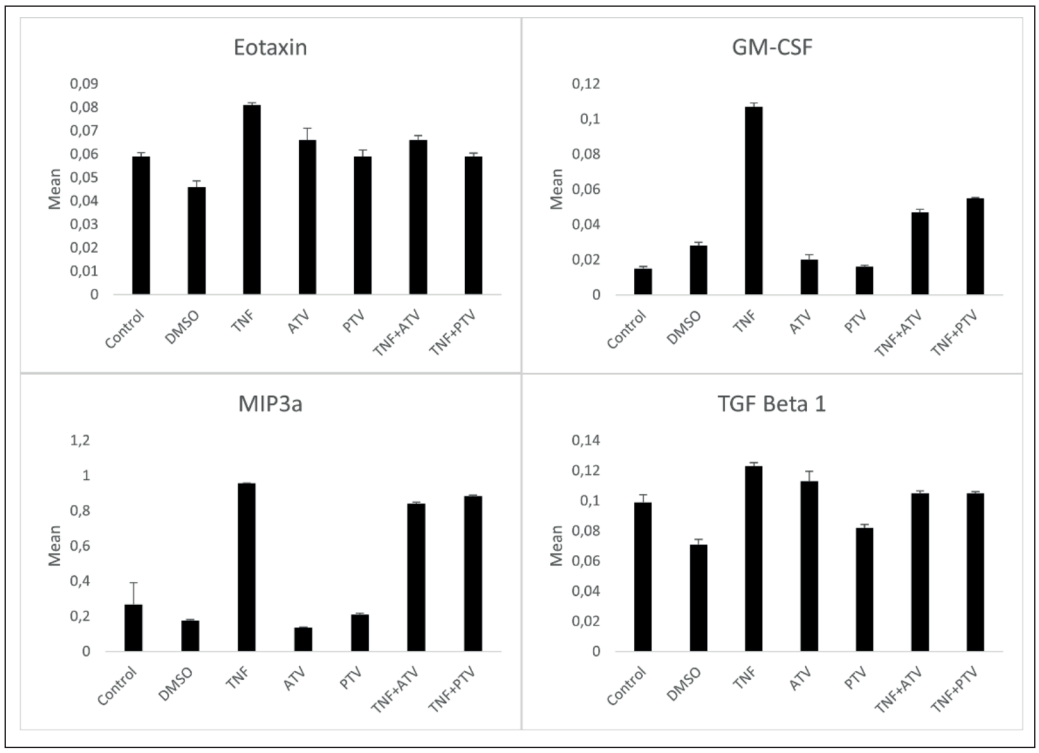

Figure 2. Graphs of the expression levels of four pro-inflammatory cytokines [eotaxin (CCL11), GMCSF (CSF2), MIP-3a (CCL20), and TGFB1] in the seven experimental groups.

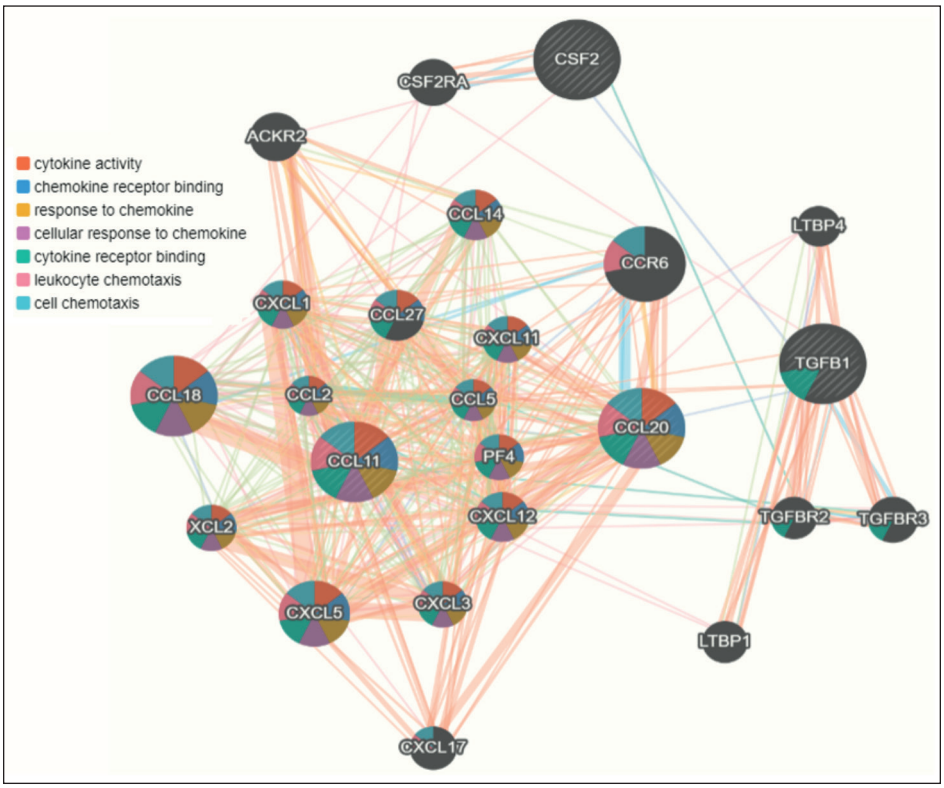

Figure 3. The results of prediction analysis for four proteins using the GeneMANIA tool. Physical interactions were detected in 77.64% of nodes, and the coexpression rates were 8.01%. Orange lines between the nodes represent possible physical contact relationships. The size of a protein symbol corresponds to the statistical significance of the interactions.

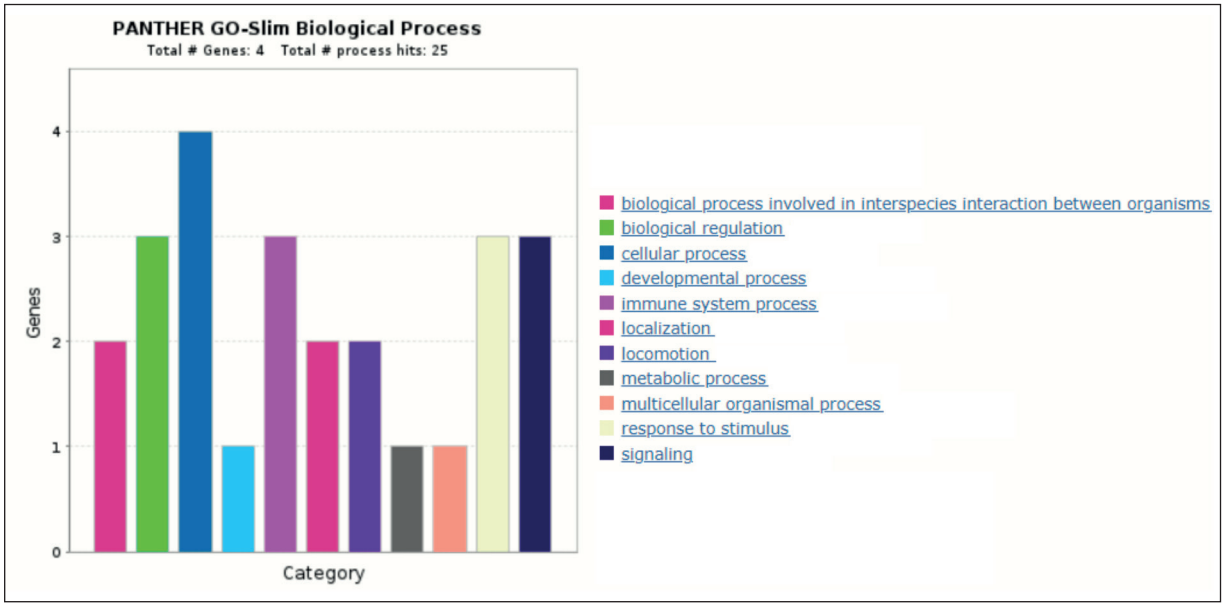

Figure 4. An overview of the results of pathway analysis using the PANTHER prediction tool for the CCL11, CCL20, GMCSF, and TGFB1 proteins.

Discussion

Compelling clinical data indicate that statins are effective medications for lowering cholesterol and meeting the treatment goals for LDL-C in individuals at a high risk of atherogenic events[19]. Currently, the realization and maintenance of LDL-C objectives are critical for the safe and successful long-term treatment of patients with hyperlipidemia. Inflammation is involved in all phases of atherogenesis, from foam cell production and plaque development to plaque rupture and thrombosis[20]. To compare the effects of statins, the present study investigated the effects of atorvastatin and pitavastatin on inflammation-related endothelial function. HSaVECs were exposed to the statins' atorvastatin (50 μM) and pitavastatin (2 μM) in the presence and the absence of TNF-alpha, an inflammation inducer. Interestingly, the results of the present study revealed that PTV (2 μM) was superior to ATV (50 μM) in reducing the levels of inflammatory markers, such as CCL11, CSF2, CCL20, and TGFB1, thus maintaining an overall endothelial function.

Since its discovery in 1982 by Bruce Roth, atorvastatin has become the most common drug used to elevate the number of "LDL receptors" on the surface of hepatocytes, thus lowering circulating lipid levels and preventing cardiovascular diseases secondary to atherosclerosis[21]. On the other hand, higher concentrations of ATV have been associated with an increase in muscle-related side events, cognitive and memory issues, and an elevation in liver enzymes[22]. In addition, ATV is predominantly metabolized *via* cytochrome P450 isoenzymes, such as CYP3A4, and is thus more likely to interact with several drugs that inhibit CYP450, notably the CYP3A4 isoenzyme. These interactions may also contribute to increased plasma concentrations of this statin, thus increasing toxicity[23].

Endothelial dysfunction is a cornerstone of atherosclerosis and predicts future cardiovascular events[24]. The results of the present study indicated that pitavastatin reduced the expression of eotaxin (CCL11), CSF2 (GM-CSF), MIP3-alpha (CCL20), and TGFB1 more effectively than atorvastatin. Eotaxin appears to increase the number of human atherosclerotic plaques[25]; GM-CSF[26] and CCL20 levels[27] are elevated under inflammatory conditions, such as atherosclerosis and associated vascular inflammation. Pitavastatin appears to enhance mRNA levels of ATP-binding cassette transporter A1 (ABCA1), which is involved in the modulation of ApoAI-mediated cholesterol efflux[28], and the expression of eNOS and thrombomodulin compared to atorvastatin. In addition, in 2002, Morikawa et al[29] suggested that pitavastatin reduces the mRNA expression of the genes associated with coagulation, inflammation, and vascular constriction, including PAI-1, endothelin-1, IL8, and MCAP-1, to maintain the overall integrity and ultrastructure of endothelial cells.

The study by Igle et al[30] expanded our understanding of pitavastatin usage since pitavastatin is only minimally metabolized *via* CYP2C9, thus decreasing the chance of toxicity caused by drug interactions. Additionally, pitavastatin metabolism by CYP2C9 is minimal, leading to a lower drug interaction-related toxicity[30]. Moreover, the accessibility of pitavastatin is higher due to its lower cost compared with that of atorvastatin[31]. Moreover, pitavastatin has pleiotropic effects that improve the structure and function of high-density lipoproteins (HDL). Compelling evidence indicates that pitavastatin induces a more pronounced elevation of HDL than atorvastatin[32].

Limitations

The main limitation of the present study is related to its *in vitro* nature. Although the model used in the present study mimics endothelial injury and prevention of atherosclerosis, *in vivo* models are needed to better understand the details of the mechanisms of action of various molecules in the prevention of atherosclerosis. In addition, further randomized prospective studies of atorvastatin in direct comparison with pitavastatin should be planned to determine which of these two statins is to be preferred.

Conclusions

Statins are extensively used agents to combat atherosclerotic cardiovascular diseases. There is a growing demand for a wider range of protection against cardiovascular risks other than an LDL-C decrease alone. Additional medication and other concurrent therapies against diabetes, aging and low HDL concentrations should not preclude these patients from getting appropriate and efficient long-term treatment for cardiovascular diseases. The results of the present study indicated that pitavastatin was more effective against atherosclerosis than atorvastatin; however, further research is warranted since there is insufficient data on the potential toxicity of pitavastatin.

Conflicts of Interest

The authors declare no conflicts of interest.

Ethics Approval

No direct involvement of subjects; hence ethical approval was not required.

Data Availability

Data may be provided on a reasonable request to the corresponding author.

Funding

Not applicable.

Authors' Contribution

BO: study concept, cell culture, writing; MA: cell culture; GY: literature review, data collection; ASD: analysis and literature review; ED: analysis and interpretation of data; DGA: analysis and interpretation of data; MU: critical revision.

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