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Beneficial Effects of Rosuvastatin and L-Arginine on High Glucose-Induced Oxidative Stress in Human Umbilical Vein Endothelial Cells

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Abstract

BACKGROUND/AIMS: The study sought to examine the impact of rosuvastatin and L-arginine, alone or in combination, on hyperglycemia-caused oxidative stress in human umbilical vein endothelial cells (HUVECs).

MATERIALS AND METHODS: HUVECs were divided into five groups: (1) control, (2) hyperglycemia, (3) hyperglycemia + rosuvastatin, (4) hyperglycemia + L-arginine, and (5) hyperglycemia + L-arginine + rosuvastatin. The incubation period was 24 hours for all study groups. Cytotoxicity assays were performed for L-arginine and rosuvastatin. After incubation with glucose, L-arginine, and rosuvastatin, malondialdehyde (MDA) level, an oxidative stress marker, and catalase activity were measured.

RESULTS: In cytotoxicity tests, the highest non-cytotoxic concentration of L-arginine and rosuvastatin was 12.5 µM. Under hyperglycemic conditions, catalase activity was significantly decreased in HUVECs (p=0.0007 versus control). L-arginine alone (p=0.0016 vs. control) and L-arginine combined with rosuvastatin (p=0.0099 vs. control) resulted in a partial increase in catalase activity. Hyperglycemia caused a significant elevation in MDA levels in HUVECs (p=0.0054 vs. control). L-arginine induced a partial reduction in MDA levels (p=0.03 vs. control), whereas the combination of rosuvastatin and L-arginine restored the altered MDA levels.

CONCLUSION: These results indicate that combined incubation with rosuvastatin and L-arginine is more effective in reducing hyperglycemia-induced oxidative stress than administration of either agent alone.

Keywords: Hyperglycemia, HUVEC, L-arginine, rosuvastatin, oxidative stress

INTRODUCTION

Diabetes is one of the most widespread diseases worldwide, significantly contributing to mortality, morbidity, and healthcare costs.[1] By 2045, the global number of people with diabetes is expected to reach approximately 693 million.[2] Diabetic complications, which include microvascular and macrovascular manifestations, are the leading causes of mortality and disability among patients with diabetes.[3]

Oxidative stress is an imbalanced redox state indicated by overproduction and accumulation of reactive oxygen species (ROS) and by impaired antioxidant mechanisms in cells or tissues.[4] Oxidative stress is a primary component of the progression of diabetic vascular disease and is strongly associated with endothelial dysfunction.[5] ROS production promotes vascular dysfunction by scavenging nitric oxide (NO) and via various direct or indirect mechanisms identified in diabetic cardiovascular disorders.[6]

L-arginine, a semi-essential amino acid present in dietary proteins,[7] is essential for the synthesis of NO, a significant vasodilator beneficial to the cardiovascular system.[8] L-arginine has been shown to reduce

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oxidative stress and superoxide radical levels in the liver and brain of diabetic rats, and in the aorta of hypercholesterolemic rabbits.[9,10] Furthermore, L-arginine supplementation ameliorated oxidative stress by reducing malondialdehyde (MDA) levels and elevating the levels of superoxide dismutase, glutathione peroxidase, and catalase in diabetic rats.[11]

Rosuvastatin is a fully synthetic lipid-lowering drug that inhibits 3-hydroxy-3-methylglutaryl-CoA reductase in cholesterol biosynthesis. Rosuvastatin is a water-soluble statin with a shorter onset of action and greater clinical efficacy.[12] Previous studies have shown that rosuvastatin improves endothelial function by reducing inflammatory responses and exerting antioxidant effects in diabetic patients.[13,14] Furthermore, the incubation with rosuvastatin reduced apoptosis and oxidative stress as well as migration in human umbilical vein endothelial cells (HUVECs) under a high concentration of glucose.[15,16]

The objective of the study was to examine the potential antioxidant efficacy of L-arginine and rosuvastatin, alone or when co-incubated in HUVECs under hyperglycemic conditions.

MATERIALS AND METHODS

The current study was performed only using commercial cell lines and *in vitro* experimental techniques. No human subjects or experimental animals were used. Consequently, the ethical committee approval and informed consent were not needed for the present study.

Chemicals

MDA, thiobarbituric acid (TBA), rosuvastatin, dimethyl sulfoxide (DMSO), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), L-arginine, and glucose were obtained from Sigma-Aldrich (Mannheim, Germany). The HUVEC cell line was obtained from the American Type Culture Collection (Manassas, VA). All materials used for cell culture [fetal bovine serum (FBS), Dulbecco's Modified Eagle's Medium (DMEM), penicillin-streptomycin, and L-glutamine] were obtained from Biowest (Riverside, MO).

Cell Lines and Experimental Groups

HUVEC, an endothelial cell line isolated from the umbilical cord vein, was used in the study. This cell line is commonly utilized in cardiovascular disease research. The cells were cultured in DMEM/F12 medium with 10% FBS, 1% L-glutamine, and 1% penicillin-streptomycin and incubated at 37 °C in 5% CO_2.

1. **For the control group, only DMEM/F12 medium was used.**
2. **Hyperglycemia group:** HUVECs exposed to 35 mM glucose for 24 h. The glucose concentration in DMEM/F12 was adjusted to 35 mM.
3. **Hyperglycemia + rosuvastatin group:** HUVECs exposed to IC_{30} dose (12.5 µM) of rosuvastatin and glucose (35 mM) for 24 h.
4. **Hyperglycemia + L-arginine group:** HUVECs exposed to IC_{30} dose (12.5 µM) of L-arginine and glucose (35 mM) for 24 h.
5. **Hyperglycemia + L-arginine + rosuvastatin group:** HUVECs were exposed to L-arginine (12.5 µM), rosuvastatin (12.5 µM), and glucose (35 mM) for 24 h.

All IC30 doses were determined by cytotoxicity assays.

Cytotoxicity

The MTT assay is commonly used to assess cell viability, proliferation, and cytotoxicity in many cell types.[17] The cells were incubated for 24 h in a medium containing glucose (0-50 mM), rosuvastatin (0-100 µM), and L-arginine (0-50 µM) in 96-well plates. Following the incubation, 100 µl of MTT solution was added to each well, and the plate was subsequently incubated for 3 hours. After removing the MTT solution, formazan crystals were dissolved in 150 µL of DMSO and mixed for 5 minutes in each well. The spectrophotometric measurement of the color intensity of this solution at 570 nm. The viability of cells in the control group was set to 100% based on their absorbance, and viability in the other groups was expressed as a percentage relative to the control.

Catalase Activity

Catalase activity in the study groups was measured by the dichromate method.[18] The procedure involves reducing dichromate dissolved in acetic acid to chromic acetate using hydrogen peroxide. The concentration of hydrogen peroxide is directly proportional to the concentration of chromic acetate generated in the process. The generated chromic acetate was quantified colorimetrically at 570 nm. The catalase activity in the study groups was quantified in kU/mg protein.

Lipid Peroxidation

MDA levels were assessed as markers of lipid peroxidation in all experimental groups.[19] The procedure involves quantifying the pink product formed by the reaction of MDA, a degradation product of lipid peroxides, with TBA, measured at 532 nm. MDA levels in the study groups were expressed in µM/mg protein.

Measurement of Protein Levels

The method is based on the principle that, under alkaline conditions, divalent copper ions react with peptide bonds in the presence of tartrate to form a complex and are reduced to monovalent copper ions. The complex is then reduced with Folin phenol reagent, and the resulting blue-violet color is measured spectrophotometrically at 540 nm to determine the protein level.[20] Protein concentrations were calculated using a standard curve and expressed as mg/mL.

Statistical Analysis

All data were analyzed by ANOVA, followed by Bonferroni's post hoc test, using GraphPad Prism 10 software (San Diego, CA). Results are expressed as mean ± standard deviation; $p<0.05$ is considered statistically significant.

RESULTS

The Viability of Human Umbilical Vein Endothelial Cells

HUVECs were exposed for 24 hours to glucose (0-50 mM), L-arginine (0-50 µM), and rosuvastatin (0-100 µM), and effects on cell viability were assessed by the MTT assay. Cell viability was expressed as a percentage relative to control cells.

The concentration of glucose causing 30% inhibition of cell viability (IC30) was determined to be 34.48 mM (Figure 1A and Table 1).

In Figure 1B, the highest dose of L-arginine that did not cause cytotoxicity was 12.5 µM. This dose was used in the *in vitro* experiments (Figure 1B).

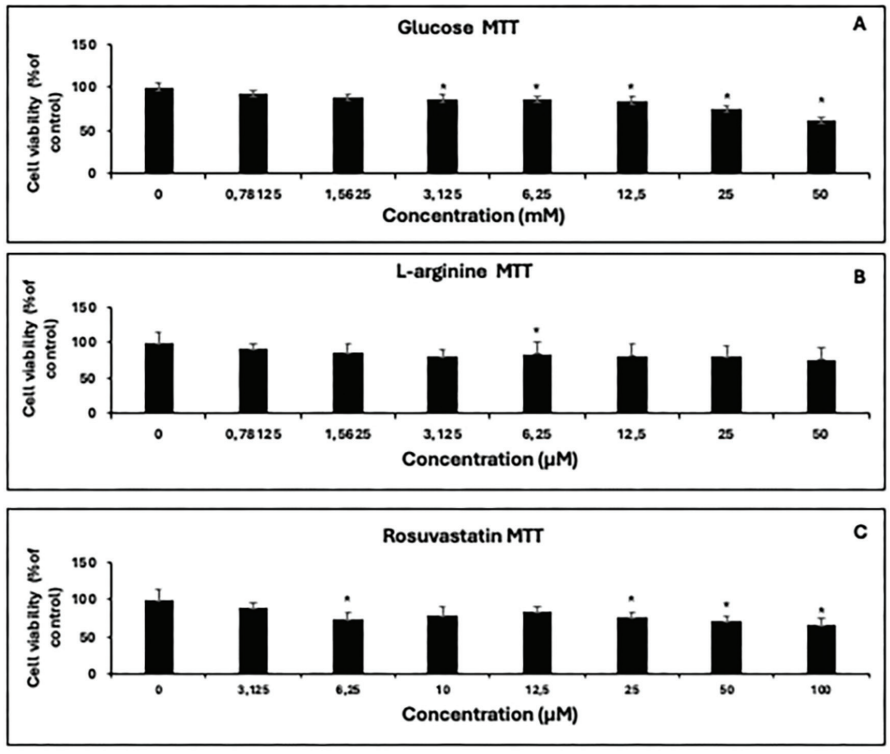

Figure 1. Cell viability at different glucose concentrations (A), different L-arginine concentrations (B), and different rosuvastatin concentrations (C) (*p<0.001 represents a statistically significant difference between the control group and each treatment dosage. Values are given as mean ± SD) (ANOVA, Bonferroni post-hoc).

MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, SD: Standard deviation, ANOVA: Analysis of variance.

Table 1. Inhibitory concentrations for glucose

	IC30 (mM)	IC20 (mM)
Glucose	34,48	18,90

The effects of rosuvastatin on the viability of HUVECs are shown in Figure 1C. Based on cytotoxicity tests, the highest dose of rosuvastatin that did not cause cytotoxicity or induce cell proliferation was 12.5 µM.

Catalase Activity

The catalase activity in all groups is shown in Figure 2 and Table 2. The hyperglycemia group (HG) group exhibited the lowest catalase activity (43%) compared with controls (p=0.0007). Incubation with rosuvastatin did not further increase this reduction [p=0.0005 vs. control; p=0.017 vs. hyperglycemia + L-arginine + rosuvastatin group (HG-R+A)]. The alteration showed a partial increase in the hyperglycemia + L-arginine group (HG-A) (p=0.0016 vs. control) and HG-R+A (p=0.0099 vs. control; p=0.035 vs. HG) groups (Figure 2, Table 2 and Supplementary Table 1).

Malondialdehyde Levels

The levels of MDA in HUVECs are displayed in Table 2 and Figure 3. The levels of MDA in the HG group were increased by 48.09% compared with controls (p=0.0054). Rosuvastatin did not reduce MDA levels (p=0.0075 vs. control). L-arginine partially decreased the increased MDA levels (p=0.03 vs. control). Combined treatment with rosuvastatin and

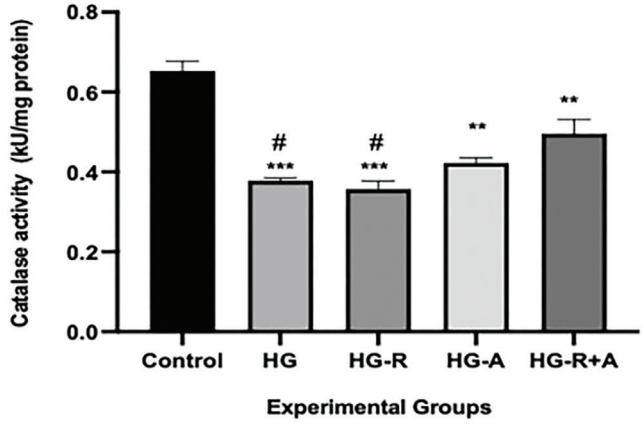

Figure 2. Catalase activity in all groups. All values are displayed as mean ± SD. **p<0.01, ***p<0.001 vs. control; #p<0.05 vs. HG-R+A. (ANOVA, Bonferroni post-hoc).

HG: Hyperglycemia group, HG-R: Hyperglycemia + rosuvastatin group, HG-A: Hyperglycemia + L-arginine group, HG-R+A: Hyperglycemia + L-arginine + rosuvastatin group, SD: Standard deviation, ANOVA: Analysis of variance.

L-arginine reversed changes in MDA levels (p=0.038 vs. HG; Figure 3, Table 2 and Supplementary Table 2).

Table 2. Catalase activity and MDA levels in HUVEC

	Control	HG	HG-R	HG-A	HG-R+A	ANOVA p-values
Catalase activity (kU/mg protein)	0.65±0.02	0.37±0.01***	0.35±0.02***	0.42±0.01**	0.50±0.03**#	0.0003
MDA levels (µM/mg protein)	10.09±0.89	14.95±0.13**	14.62±0.11**	13.38±0.47*	11.80±0.92#	0.0024

*p<0.05, **p<0.01, ***p<0.001 vs. control; #p<0.05 vs. HG. All values are presented as mean ± SD. (ANOVA, Bonferroni post-hoc).
HG: Hyperglycemia group, HG-R: Hyperglycemia-rosuvastatin group, HG-A: Hyperglycemia-L-arginine group, HG-R+A: Hyperglycemia-L-arginine + rosuvastatin group, SD: Standard deviation, MDA: Malondialdehyde, ANOVA: Analysis of variance.

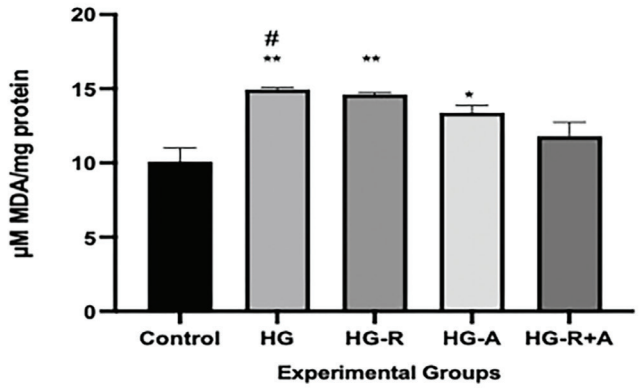

Figure 3. MDA levels in all groups. All values are displayed as mean ± SD. *p<0.05, **p<0.01 vs. control; #p<0.05 vs. HG-R+A. (ANOVA, Bonferroni post-hoc).

MDA: Malondialdehyde, HG: Hyperglycemia group, HG-R: Hyperglycemia + rosuvastatin group, HG-A: Hyperglycemia + L-arginine group, HG-R+A: Hyperglycemia + L-arginine + rosuvastatin group, SD: Standard deviation, ANOVA: Analysis of variance.

DISCUSSION

The current study has demonstrated that combined incubation of HUVEC with rosuvastatin and L-arginine is likely to be more effective at reducing hyperglycemia-induced oxidative stress than rosuvastatin or L-arginine alone.

High blood glucose contributes significantly to endothelial dysfunction in diabetes mellitus.[21] Recent data reveal that increased glucose levels significantly affect endothelial cells, thereby contributing to the clinical complications of type 2 diabetes mellitus. In the current study, HUVECs were incubated in high glucose (35 mM) for 24 hours to model diabetes mellitus *in vitro*. High-glucose-induced oxidative stress in HUVECs was consistent with earlier studies.[22-24]

According to the results of cytotoxicity tests, the highest doses of rosuvastatin and L-arginine that did not cause cytotoxicity or induce cell proliferation were 12.5 µM. In a previous study, rosuvastatin at concentrations of 0.01, 0.1, and 1 µM did not induce apoptosis in HUVECs incubated with oxidized low-density lipoprotein.[25,26] Furthermore, rosuvastatin at 10 µM improved endothelial integrity during incubation with 5-hydroxycholesterol.[27] In addition, L-arginine at a concentration of 12.5 µM did not cause cytotoxicity in HUVECs. Direct data on the cytotoxicity of 12.5 µM L-arginine in HUVECs are not explicitly detailed in the search results. Additionally, Scalera et al.[28] showed that L-arginine alleviated cytotoxicity at millimolar concentrations. Lower micromolar concentrations, such as 12.5 µM, are unlikely to be cytotoxic.

In the current study, HUVECs exposed to high glucose concentrations showed a considerable elevation in MDA levels and a decrease in catalase activity. Similarly, previous studies indicate that hyperglycemia increases oxidative stress in HUVECs, which implies increased MDA levels and decreased catalase activity.[29-32] Furthermore, incubation with rosuvastatin or L-arginine alone partially reversed the alterations, whereas combined administration produced the most significant improvement. In addition, previous data showed that rosuvastatin exerted partially protective antioxidant effects in renal tissue of diabetic rats.[33] Also, rosuvastatin decreased MDA levels and enhanced catalase activity, thereby mitigating oxidative stress and improving oxidizedlowdensity lipoprotein-induced endothelial dysfunction in HUVECs.[26] Furthermore, in studies of alloxan-induced diabetic rats, L-arginine treatment lowered MDA levels and increased catalase activity in gastrointestinal tissues and blood, suggesting protective antioxidant effects against diabetic oxidative stress.[11,34]

Study Limitations

The current study has some limitations. First, measurements of oxidative stress were limited to MDA and catalase activity. Although these are well-established indicators of lipid peroxidation and antioxidant response, inclusion of additional markers such as intracellular ROS production, superoxide dismutase, glutathione peroxidase, and NO-related parameters may provide enhanced mechanistic insight. Second, protein or gene expression levels of oxidative stress markers could not be analyzed; therefore, the involvement of pathways, such as endothelial NO synthase and antioxidant signaling, is inferred rather than directly demonstrated. Furthermore, the findings were obtained from experiments using a single endothelial cell line (HUVECs) at a single time point with only a 24-hour exposure. Despite these limitations, the study provides initial evidence supporting the observed effects; future studies incorporating broader oxidative stress profiling, molecular analyses, and additional models are warranted.

CONCLUSION

These findings indicate that combined incubation with rosuvastatin and L-arginine is more effective than either agent alone in reversing hyperglycemia-induced oxidative stress. Further studies are necessary to evaluate the therapeutic effects of the combination in preventing diabetic complications in preclinical models.

MAIN POINTS

- High glucose exposure increases the levels of malondialdehyde and decreases catalase activity in in human umbilical vein endothelial cells (HUVECs).
- The highest non-cytotoxic concentration for both rosuvastatin and L-arginine in HUVECs was 12.5 µM, ensuring safety and effectiveness at this dose in vitro.
- Combined incubation with rosuvastatin and L-arginine significantly reduces hyperglycemia-induced oxidative stress in HUVECs more effectively than either treatment alone.

ETHICS

Ethics Committee Approval: The author declare that the materials and methods used in the current study do not need approval from an ethics committee or special legal permission.The study was not conducted on humans or experimental animals.

Informed Consent: The study did not include human participants or samples. Informed consent was not applicable.

DISCLOSURES

Financial Disclosure: The author declared that this study received no financial support.

Supplementary Material: https://d2v96fxpocvxx.cloudfront.net/58770459-5a06-4076-a747-5b73e24cd7c0/content-images/04cfcfca-74dd-4e46-96e7-81e1d688343e.pdf

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