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Original article

Efficiency of hepatocyte pretreatment with coenzyme Q_{10} against statin toxicity

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Statins are potent cholesterol-lowering drugs that can have serious adverse effects on the muscles and liver. The aim of our *in vitro* study was to establish the protective effect of coenzyme Q_{10} (CoQ_{10}, in its optimal dose of 200 μmol L^{-1}) against cytotoxicity induced by atorvastatin, simvastatin, and lovastatin in isolated rat hepatocytes by observing parameters such as cell death, reactive oxygen species formation, lipid peroxidation, mitochondrial membrane potential, and cellular reduced and oxidised glutathione content. Our findings have shown that pretreatment with CoQ_{10} was effective in reducing the toxic effects of statins in rat hepatocytes. This work demonstrates that the addition of CoQ_{10} to statin treatment regimens may protect hepatocytes (and also other types of cells) from statin-induced injuries and alleviate their side effects.

KEY WORDS: *atorvastatin; hepatotoxicity; lipid peroxidation; lovastatin; oxidative stress; reactive oxygen species; simvastatin; ubiquinone*

While the effects of statins in reducing the risk of cardiovascular disease are well established, less is known about their risks, side effects (1), and toxicity (2–5).

Coenzyme Q_{10} (CoQ_{10}), also known as ubiquinone, is a potent antioxidant, membrane stabiliser (6), and an integral cofactor in the mitochondrial respiratory chain (7) that helps to generate adenosine triphosphate (ATP) (8). It may also regulate genes associated with cell metabolism (9, 10), and its depletion may have a role in statin-induced myalgia (11, 12).

In several clinical studies Q_{10} was supplemented to statins to see whether Q_{10} would decrease statin-induced side effects (10, 13, 14). These studies were small and underpowered, and have found no protective effect of Q_{10} supplementation.

Based on our earlier *in vitro* finding (4) of statin hepatotoxicity through reactive oxygen species (ROS) formation and consequent oxidative stress and on the evidence of reduced oxidative stress in hepatocytes treated with different antioxidants (15), this study aimed to establish the protective role of CoQ_{10} against statin toxicity in rat hepatocytes by observing its effects on parameters such as ROS formation, lipid peroxidation (LPO), mitochondrial membrane potential, cellular reduced and oxidised glutathione (GSH/GSSG), and cell viability. Our secondary aim was to establish whether these effects were time-dependent or not.

MATERIALS AND METHODS

Chemicals

Atorvastatin, simvastatin, lovastatin, CoQ_{10}, rhodamine 123, 5,5′-dithio-bis (2-nitro-benzoic acid) (DTNB), 2',7'-dichlorofluorescin diacetate (DCF),

glutathione reductase from baker's yeast, β-nicotinamide adenine dinucleotide (NADPH), and collagenase from *Clostridium histolyticum* were purchased from Sigma-Aldrich (St. Louis, MO, USA). 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES), 2-vinylpyridine, triethanolamine, and oxidised glutathione (GSSG) were obtained from Acros (New Jersey, NJ, USA). Bovine serum albumin was purchased from Roche Diagnostics (Indianapolis, IN, USA). Ethyleneglycol-bis(ρ-aminoethyl ether)-N,N,N′,N′-tetraacetic acid (EGTA), N-methylthiourea, trichloroacetic acid (TCA), and trypan blue were obtained from Merck (Darmstadt, Germany). Thiobarbituric acid was obtained from SERVA (Heidelberg, Germany). All salts used for preparing buffer solutions were of analytical grade and obtained from Merck.

Hepatocyte isolation

Hepatocytes were isolated from 18 male Sprague-Dawley rats (weighing 250–300 g) raised at Tabriz University of Medical Sciences, Tabriz, Iran, caged in standard conditions (temperature 21–23 °C, relative humidity 50–60 %) and fed on standard chow diet with free access to water. The animals were handled and used according to the animal handling protocol of Tabriz University of Medical Sciences, approved by a local ethics committee.

The procedure involved two-step collagenase perfusion as described by Moldeus et al. (16). About 85–90 % of hepatocytes were viable at the time of isolation, as established by the trypan blue uptake test (17). Viable cells were suspended in Krebs-Henseleit buffer ($1x10^6$ cells mL^{-1}) containing 12.5 mmol L^{-1} of HEPES and incubated under a stream of carbogen gas (95 % O_2 and 5 % CO_2) in continuously rotating round-bottomed 50 mL flasks at 37 °C. Hepatocytes were kept under these conditions for 30 min to achieve equilibrium between the gas and liquid phases before the addition of chemicals.

Cell viability and treatment doses

The viability of cells treated with atorvastatin, simvastatin, lovastatin, and CoQ_{10} was assessed using the trypan blue (0.1 %, w/v) uptake test described elsewhere (17) at incubation hour one, two, and three. For this test, atorvastatin, simvastatin and/or CoQ_{10} were dissolved in methanol and lovastatin in dimethyl sulphoxide. The maximum volume of the solvent was 20 μL. In the absence of statins, none of the solvents affected hepatocyte viability at the concentrations used.

As described elsewhere (4), LC_{50} was a drug concentration which caused 50 % cell death after 120 min of incubation. For atorvastatin it was 450 μmol L^{-1}, for simvastatin 200 μmol L^{-1}, and for lovastatin 200 μmol L^{-1}.

By trying out different doses of CoQ_{10}, we found that the optimum effective dose of CoQ_{10} was 200 μmol L^{-1}. We then experimented with treatment times by adding this optimal CoQ_{10} dose 30 min before statins, at the same time with statins, and 30 min after statins. The most effective timing was 30 min before statins (data not shown). In other words, all further experiments in this study were carried out with 200 μmol L^{-1} of CoQ_{10} added 30 min before statins. These concentrations are much higher than those found in serum during statin treatment which is in the range of 1–10 nmol L^{-1} (18).

We used the accelerated cytotoxicity mechanism screening (ACMS) technique with freshly isolated rat hepatocytes to explore the mechanisms of statin-induced toxicity and possible protective effects of CoQ_{10}. This technique is useful and important in determining the cytotoxic effectiveness of a drug or xenobiotic in a freshly isolated rat hepatocyte suspension over two to three hours. A major advantage of ACMS is that a high drug dose over these two to three hours exhibits the same hepatotoxicity *in vitro* as would a lower drug dose over a longer period of time (24 to 48 h) exhibit *in vivo* (19, 20). In other words, this method can be used to characterise and predict hepatotoxicity *in vivo*.

ROS formation

ROS formation was measured as described earlier (21). In short, we added 1.6 μmol L^{-1} of DCF to hepatocytes incubated with statins, where it hydrolysed to non-fluorescent dichlorofluorescein (DCFH) and then reacted with ROS to form highly fluorescent DCFH. Fluorescence intensity was measured in 1 mL of hepatocyte suspension (10^6 cells) using a Jasco® FP-750 spectrofluorometer (Jasco Corporation, Tokyo, Japan) at excitation and emission wavelengths of 500 and 520 nm, respectively.

LPO assay

Lipid peroxidation was determined using the thiobarbituric acid reactive substances (TBARS) assay, which measures aldehydes formed by

degradation of lipid hydroperoxides. Absorbance was recorded by a Pharmacia Biotech Ultrospec® 2000 spectrophotometer (Cambridge, UK) at 532 nm after treating 1.0 mL aliquots of hepatocyte suspension (10^6 cells mL^{-1}) with trichloroacetic acid (70 %, w/v) and boiling the supernatant with thiobarbituric acid (0.8 %, w/v) for 20 min (22).

Cellular GSH/GSSG

Reduced and oxidised glutathione (GSH and GSSG) hepatocyte levels were determined using the enzymatic recycling method (23). To determine GSH, we took 1 mL aliquots of suspended cells (10^6 cells mL^{-1}) and centrifuged them with 2 mL of 5 % trichloroacetic acid. Then we added 0.5 mL of Ellman's reagent (0.0198 % DTNB in 1 % sodium citrate) and 3 mL of phosphate buffer (pH 8.0). The absorbance of developed colour was determined at 412 nm using a Biotech Pharmacia Ultrospec® 2000 spectrophotometer.

To assess hepatocyte GSSG levels, we first bonded cellular GSH with 2-vinylpyridine and then neutralised the excess of 2-vinylpyridine with thriethanolamine. GSSG was then reduced to GSH with glutathione reductase and NADPH. The amount of GSH formed in this way was measured as described above (23).

Mitochondrial membrane potential assay

Mitochondrial membrane potential (MMP) was assessed by monitoring the uptake of rhodamine 123, as described elsewhere (24, 25). Isolated cells were extracted and then resuspended in their original media containing 1.5 μmol L^{-1} of rhodamine 123. After 10 min of incubation, the cells were centrifuged and supernatant absorption measured with a Jasco® FP-750 spectrofluorometer. The amount of dye remaining in the supernatant was inversely proportional to MMP. The results are reported as the difference in fluorescence intensity between control and treated cells and expressed as percentage of control.

Statistical analysis

The chi-square test was used for cell viability, cellular GSH, and MMP. One-way analysis of variance, followed by Tukey's *post-hoc* test, was used for LPO and ROS formation. A p-value of <0.05 was considered significant.

RESULTS

Results are shown as mean±standard error (SE) of marker measurements from at least three separate experiments. The cell viability test (with trypan blue) showed that atorvastatin, simvastatin, and lovastatin were toxic to hepatocytes in a time-dependent manner (Table 1). The most toxic was simvastatin, but CoQ_{10} effectively reduced cell death induced by all the statins. Statins significantly depleted cellular glutathione reservoirs (Figure 1) and increased the levels of oxidised glutathione (Figure 2), which is an indicator of oxidative stress (22). Thirty-minute pretreatment of hepatocytes with CoQ_{10} significantly lowered GSSG and increased GSH levels (Figure 1

Table 1 *Protective effect of pretreatment with CoQ_{10} against statin-induced cytotoxicity in isolated rat hepatocytes expressed as percentage of trypan blue uptake (mean±SD)*

Treatment	Incubation time / min		
	60	120	180
Control	18±1	22±1	24±1
CoQ_{10} 200 μmol L^{-1}	15±1	17±1	19±2
Atorvastatin 450 μmol L^{-1}	36±1[a]	52±2[a]	68±1[a]
+ CoQ_{10} 200 μmol L^{-1}	28±1	35±2[b]	49±2[b]
Simvastatin 200 μmol L^{-1}	38±2[a]	54±2[a]	88±2[a]
+ CoQ_{10} 200 μmol L^{-1}	34±3	41±4[b]	59±3[b]
Lovastatin 200 μmol L^{-1}	39±2[a]	52±2[a]	74±5[a]
+ CoQ_{10} 200 μmol L^{-1}	30±3	37±2[b]	53±5[b]

[a] *Significantly different from control (n=3, chi-square,* $p<0.05$*);* [b] *Significantly different from statin-treated group (n=3, chi-square,* $p<0.05$*)*

and Figure 2). Similarly, statins significantly increased ROS formation, and CoQ_{10} pretreatment effectively attenuated the process (Figure 3). The same is true for LPO (Figure 4), confirming earlier findings (26). Statins also decreased MMP in respect to control cells, while CoQ_{10} (200 μmol L^{-1}) pretreatment effectively countered their effects (Figure 5).

DISCUSSION

Our study has confirmed the beneficial, cytoprotective effects of CoQ_{10} against statin-induced oxidative stress, as it significantly improved all the

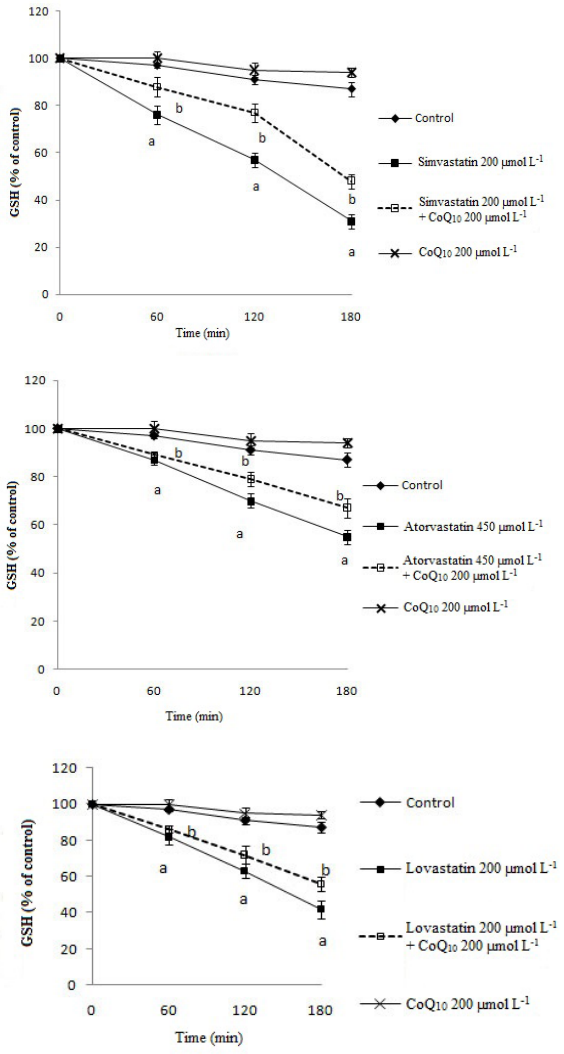

Figure 1 *Statin-induced GSH depletion in isolated rat hepatocytes and the protective effect of CoQ_{10}*
a: significantly different from control (n=3, chi-square, p*<0.05); b: significantly different from the statin-treated group (n=3, chi-square,* p*<0.05)*

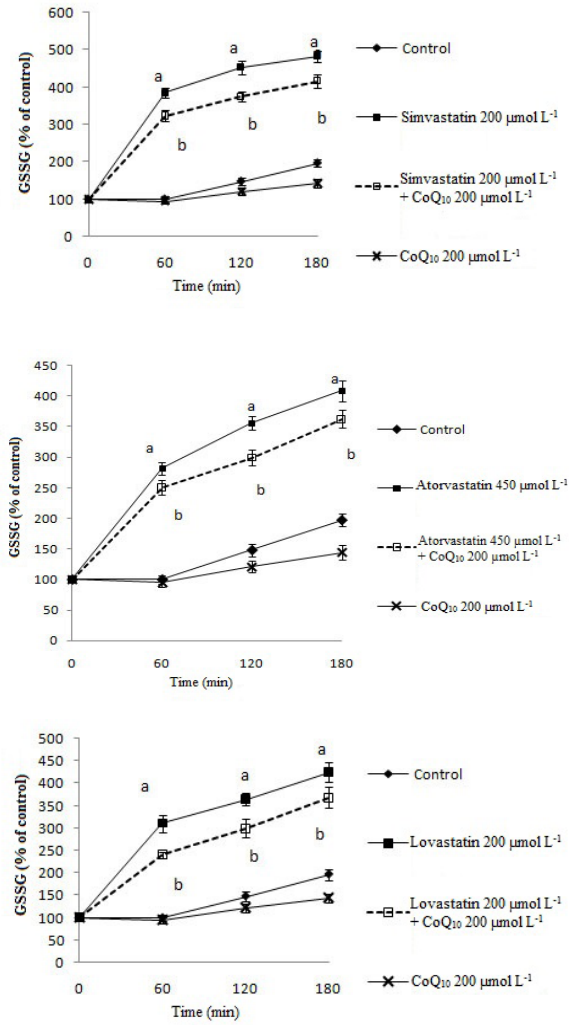

Figure 2 *Statin-induced GSSG elevation in isolated rat hepatocytes and the protective effect of CoQ_{10}*
a: significantly different from control (n=3, chi-square, p*<0.05); b: significantly different from the statin-treated group (n=3, chi-square,* p*<0.05)*

investigated parameters. We already know that CoQ_{10} participates in the electron transport chain in mitochondria (27) and that statins can interfere with CoQ_{10}, compromising cellular energy production (28). La Guardia et al. (29) have demonstrated that simvastatin inhibits mitochondrial respiration, depletes CoQ_{10}, and increases hydrogen peroxide production. A small increase in CoQ_{10} concentration in mitochondrial membranes can therefore restore mitochondrial respiration (7) as one of the mechanisms to protect liver cells from statin toxicity.

The second fundamental property of CoQ_{10} involves its antioxidative (free radical scavenging) function (30, 31). The efficacy of CoQ_{10} treatment against mitochondrial dysfunction induced by beta

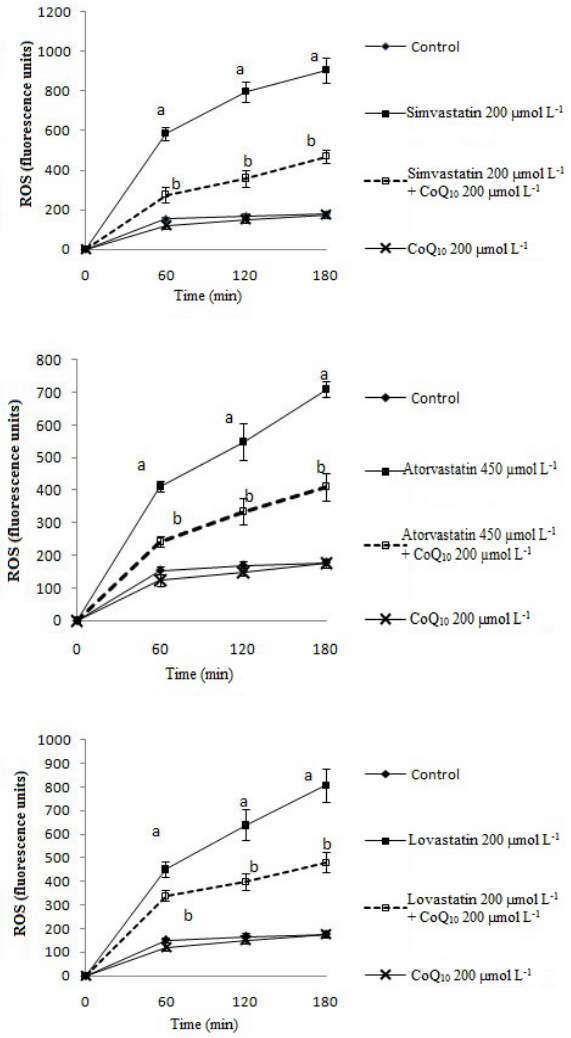

Figure 3 *Statin-induced ROS formation in isolated rat hepatocytes and the protective effect of CoQ_{10}*
a: significantly different from control (n=3, ANOVA, p*<0.05);*
b: significantly different from the statin-treated group (n=3, ANOVA, p*<0.05)*

amyloid has been evaluated in the brains of diabetic rats, where CoQ_{10} treatment attenuated the decrease in oxidative phosphorylation and prevented increased hydrogen peroxide production (32). This effect, in addition to its role in mitochondria, may be due to the ability of CoQ_{10} to scavenge free radicals and reactive metabolites produced during statin metabolism, which is also supported by lower ROS formation, MMP, LPO, and GSH oxidation in our experiments.

Ali et al. (33) have shown that L-carnitine and CoQ_{10} have a pronounced prophylactic effect against liver damage induced by halogenated alkanes such as carbon tetrachloride (CCl_4). In that study, the investigators pretreated rats with CoQ_{10} 24 h before the administration of CCl_4. This is in accordance with our finding that the best protection was achieved with CoQ_{10} pretreatment. Most toxins start by affecting the cytoplasm. However, the major site of action for CoQ_{10} is the mitochondrion, where it is needed for electron transfer in mitochondrial respiration. If CoQ_{10} is consumed in the cytoplasm as an antioxidant, it will fall short of its role in the mitochondrial respiratory chain. However, if CoQ_{10} abounds in the mitochondria before toxic effects take place, it will be able to counteract both the reactive metabolites in the cytoplasm and ROS produced in the mitochondria.

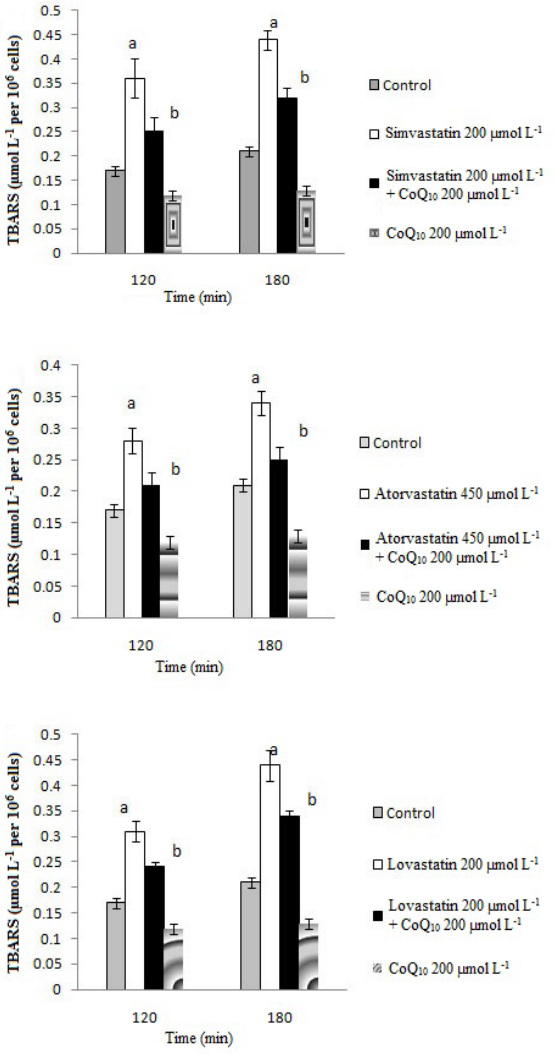

Figure 4 *Statin-induced lipid peroxidation in isolated rat hepatocytes and the protective effect of CoQ_{10}*
a: significantly different from control (n=3, ANOVA, p*<0.05);*
b: significantly different from the statin-treated group (n=3, ANOVA, p*<0.05)*
TBARS-thiobarbituric acid reactive substances

While the ACMS method we used in our *in vitro* experiments may have minor limitations related to short incubation time (34), it simulates *in vivo* effects of statins and CoQ_{10} pretty well (19, 20). However, only clinical trials will be able to answer which CoQ_{10} dose and timing provide the best protection against statin-related side effects in humans.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

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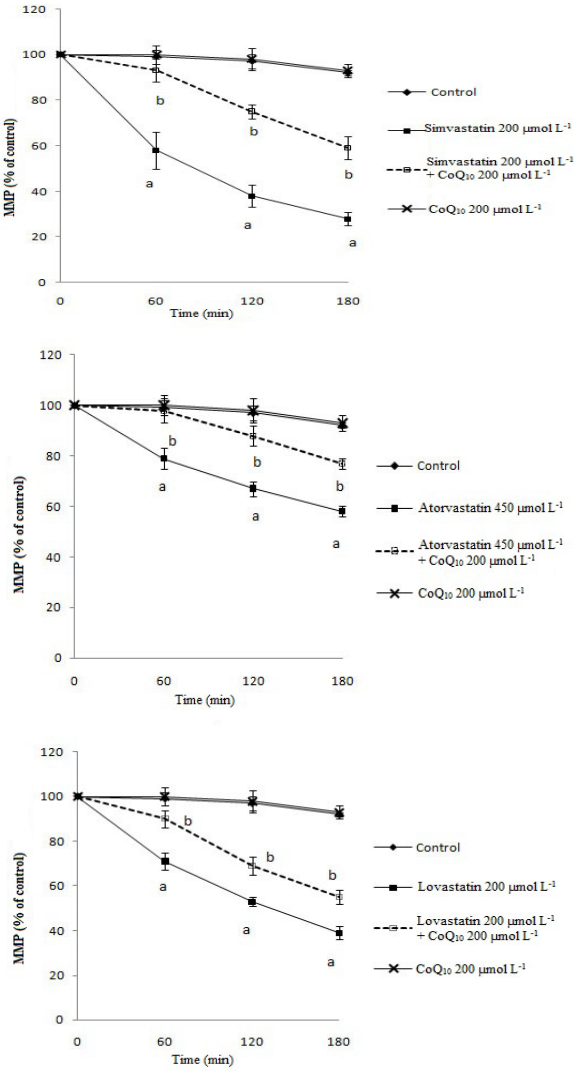

Figure 5 *Statin-induced mitochondrial membrane potential (MMP) reduction in isolated rat hepatocytes and the protective effect of CoQ_{10}*
*a: significantly different from control (*n*=3, chi-square,* p*<0.05); b: significantly different from the statin-treated group (*n*=3, chi-square,* p*<0.05)*

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Sažetak

Djelotvornost predtretmana štakorskih hepatocita koenzimom Q_{10} protiv toksičnosti statina

Statini su snažni lijekovi za snižavanje kolesterola, koji mogu izazvati ozbiljne nuspojave u mišićima i jetrima. Svrha je ovog *in vitro* istraživanja bila utvrditi zaštitno djelovanje koenzima Q_{10} (CoQ_{10}, u optimalnoj dozi od 200 μmol L^{-1}) protiv citotoksičnosti atorvastatina, simvastatina i lovastatina u izoliranih štakorskih hepatocita kroz parametre poput vijabilnosti, nastanka reaktivnih kisikovih čestica, lipidne peroksidacije, potencijala mitohondrijske membrane te reduciranog i oksidiranog glutationa. Rezultati su pokazali da predtretman štakorskih hepatocita CoQ_{10} djelotvorno ublažava toksične učinke statina te da bi njegovo kombiniranje sa statinima moglo zaštititi hepatocite (i druge vrste stanica) od oštećenja izazvanih statinima te ublažiti nuspojave povezane s ovim lijekovima.

KLJUČNE RIJEČI: *atorvastatin; hepatotoksičnost; lipidna peroksidacija; lovastatin; oksidativni stres; reaktivne kisikove čestice; simvastatin; ubikvinon*

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