HIGH GLUCOSE LEVELS ABOLISH ANTIATHEROSCLEROTIC BENEFITS OF ACE INHIBITION IN ALLOXAN-INDUCED DIABETES IN RABBITS


The renin-angiotensin system (RAS) is linked to the pathophysiology of many conditions present in diabetes, such as hypertension, dyslipidemia, and central obesity and studies have demonstrated the benefits of RAS blockade not only in reducing blood pressure, but also in decreasing the risk of cardiovascular, renal, and cerebrovascular diseases [1,2].

RAS has been well recognized as a complex and relevant cellular pathway capable of inducing attenuation of the atherosclerosis development through RAS blockade by either ACE inhibitors or AT1 blockers. The use of these antihypertensives seems to recover endothelial function [3,4], to diminish inflammation [5,6], and to improve insulin sensitivity [7,8].

In recent years, prospective studies showed that these antihypertensives are capable of preventing new-onset diabetes and its cardiovascular complications. In the Heart Outcomes Prevention Evaluation (HOPE) trial Micro-HOPE substudy, diabetic patients treated with ramipril had significant reductions in these endpoints and, compared with the overall population, had greater relative reductions in cardiovascular death (37% versus 26%, respectively) and total mortality (24% versus 16%, respectively), versus amlodipine. However, the most interesting finding of this study was that among patients without diabetes, when treated with ramipril, there was a 34% decrease in the risk for new-onset diabetes [9]. In another study (Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial), losartan treatment was accompanied by a 13% reduction in the risk of primary end point. This benefit, however, was more pronounced among diabetics, with a significant 24% reduction in the primary end point [10]. These findings suggest that diabetic patients may have a particular benefit from angiotensin receptor blocking agent, as well. Furthermore, the risk of new-onset diabetes was reduced 25% among non-diabetics [11], which may be related to their anti-oxidative properties, among others.

Several mechanisms have been proposed to explain these findings, mainly by reducing the amount of tissue angiotensin II [12]. In fact, in the presence of RAS activation, some authors have proposed changes in the insulin receptor substrate phosphorylation in serine instead of
threonine, leading to impairment of glucose transporter translocation [13]. In addition, angiotensin II may cause many cellular alterations related to the development of atherosclerosis [14], including endothelial dysfunction, increased oxidative stress [15,16], reduced nitric oxide availability [17], and hemostasis disturbances [18,19].

We performed a study investigating the effects of the angiotensin-converting enzyme (ACE) inhibitor quinapril on the development of atherosclerosis in rabbits with hypercholesterolemia and alloxan-induced diabetes [20]. In this study, diabetes was induced in New Zealand male rabbits with a single dose of alloxan (100 mg/kg, i.v.) and, according to plasma glucose levels obtained after one week, the animals were divided in two groups (≥ 250 mg/dL GI, GII or < 250 mg/dL GIII, GIV). One group of animals that were initially hyperglycemic but presenting < 250 mg/dL glucose at the end of study formed the GV. All animals received 0.5% cholesterol-enriched diet for 12 weeks. Each group was randomly assigned to receive (GII, GIV, GV) or not (GI, GIII) quinapril (30 mg/day) added to hypercholesterolemic diet. After 12 weeks, animals with baseline high glucose levels after one week of alloxan treatment and whose glucose levels remained high at the end of the experiment (GI, GII) presented hypertriglyceridemia (p < 0.02 versus basal). Plasma ACE activity was lower in quinapril-treated animals (p < 0.01 versus untreated groups). However, aorta intima/media ratio, intima area, and plaque thickness were lower only in the subgroups of quinapril-treated animals with low glucose levels (GIV, GV) (p < 0.05) (Figure 1). Analyzing the aorta histology, it was verified that disarrangement in the media layer adjacent to internal elastic lamina were less prevalent among GIV rabbits than in the other groups (p = 0.01).

![Figure 1. Intima/media ratio in aorta of rabbits with hypercholesterolemia and alloxan-induced diabetes, treated with ACE inhibitor.](image)

* p < 0.01, GIV < GIII; ** p < 0.05, GV < GIII (ANOVA-Newman-Keuls). The bars represent mean values ± SEM of I/M ratio

In conclusion, cholesterol-induced atherosclerosis in rabbits was reduced when treated with quinapril, a benefit that was abolished in the presence of high glucose plasma levels. In addition, attenuation of atherosclerosis could also be obtained in previously hyperglycemic animals, suggesting an important role for glucose plasma control, apparently essential for the whole benefit of an ACE inhibitor in this model of diabetes and atherosclerosis.

Recently, the beneficial role of ACE inhibition regarding endothelial function and atherosclerosis, using the rabbit model of cholesterol-induced atherosclerosis, was abolished by the concomitant use of hydrochlorothiazide, suggesting that diuretics may promote alterations in
cellular signaling related to RAS [21]. In our previous study among hypercholesterolemic rabbits treated with statin [22] we observed less advanced plaques comparing with rabbits without treatment. In a study with rabbits treated with either statin or ACE inhibitor [23] other authors observed that both drugs enhanced acetylcholine-induced relaxation, reduced intimal thickening, and improved fibrinolytic balance in atherosclerotic rabbits in a similar manner. However, only the combination of both drugs was able to prevent the increase in inflammatory markers induced by hypercholesterolemia, suggesting that the association of both drugs may provide a synergistic effect on vascular inflammation.

Our results support the hypothesis that high plasma glucose may abolish the antiatherosclerotic effect of ACE inhibitors, suggesting that other mechanisms beyond ACE activation should develop for the treatment of atherosclerosis.

References