

THE EFFECTS OF CAPTOPRIL AND AMLODIPINE ON C-REACTIVE PROTEIN CONCENTRATIONS IN TYPE 2 DIABETIC HYPERTENSIVE PATIENTS

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ABSTRACT

Objective: To compare the effects of the ACE inhibitor captopril with the calcium channel blocker amlodipine on serum CRP concentrations in hypertensive type 2 diabetic patients.

Methodology: This is a case control study conducted in Al-Wafa Diabetic Center in Mosul. Serum CRP concentrations were measured in two groups of hypertensive type 2 diabetic patients before and after drug administration (group 1 on captopril therapy, group two on amlodipine therapy).

Results: A significant reduction of serum CRP level was demonstrated after treatment with captopril but not with amlodipine. Mean CRP concentration of the control group was statistically lower than those of captopril and amlodipine groups.

Conclusion: The present study showed that hypertensive type 2 diabetic patients are associated with increased level of CRP and therapy with captopril but not amlodipine significantly reduced CRP, suggesting a possible anti-inflammatory action of captopril in addition to its BP lowering effects thus captopril may be regarded as the drug of choice in the treatment of BP in diabetic hypertensive patients.

KEY WORDS: Hypertension, Type 2 diabetes mellitus, C-reactive protein, Captopril, Amlodipine.

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INTRODUCTION

C-reactive protein (CRP) is an acute phase protein produced primarily by the liver in response to inflammatory cytokines such as interleukin-6 and is elevated in inflammatory states.¹ C-reactive protein plays a role in the pathogenesis of cardiovascular disease. It is a

marker and predictor of cardiovascular disease. Higher levels of CRP predict cardiovascular disease in asymptomatic men and women in the general population, indicating a possible role for inflammation in the etiology of cardiovascular disease.²⁻⁴ Reports indicating that CRP levels are elevated during acute cardiovascular and cerebrovascular events, may suggest that CRP has value in predicting the subsequent occurrence of such events.^{5,6}

A growing body of data reinforces the concept that inflammation plays an important role in the pathogenesis of type II diabetes⁷⁻⁹ and several studies demonstrate that CRP can be used to predict the development of type II diabetes mellitus.^{8,10,11} In the nearly 6000 participants in the Cardiovascular Health Study whose circulating levels of inflammatory mark-

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ers were determined both at baseline and after 3-4 years of follow up, those who developed diabetes had higher measured levels of CRP than those who remained euglycemic. In addition, those with elevated levels of CRP were found more likely to develop diabetes over the course of the study.¹² A number of other studies can also be demonstrated that CRP can act as a risk factor for the development of diabetes and that CRP levels increased in diabetic patients.^{8,13} It seems that CRP is useful for identifying patients with, or who are at risk of developing diabetes and the metabolic syndrome.⁸ The components of the metabolic syndrome are midline obesity, elevated triglycerides, decreased HDL cholesterol, hypertension and glucose intolerance. Levels of CRP correlate with these individual components and provide additional prognostic informations regarding disease severity.¹⁴

Markers of inflammation such as CRP were shown to be elevated in patients with hypertension.¹⁵ The association between hypertension and CRP levels was marginally significant. In addition there was a significant tendency for hypertension to increase with increased CRP level.¹⁶ Experimental data and results from cross-sectional studies in humans indicate a relationship between CRP levels and blood pressure.¹⁷ Plasma CRP concentration was greater in hypertensive individual than in control individuals.¹⁸

Many drugs have been found to reduce CRP levels in addition to their primary therapeutic effects. Clinical trials have shown that statins reduce patient levels of CRP by 15% to 28% as early as six weeks after treatment begins, independent of the magnitude of reduction in LDL- Cholesterol level.¹⁹⁻²¹ Another drugs that may reduce CRP levels including: aspirin, rofecoxib, celecoxib, clopidogrel, fenofibrate, vitamin E, valsartan, telmisartan, rosiglitazone and pioglitazone²² and beta adrenoceptor antagonists.²³

Clinical data on the effects of ACE inhibitors and calcium antagonists on serum CRP concentrations are limited, and information in hypertensive patients with type II diabetes

mellitus is virtually lacking, The primary objective of this trial was to compare the effects of the ACE inhibitor captopril with the calcium antagonist amlodipine on serum CRP concentrations in patients with type II diabetes and hypertension. Blood pressure was measured as secondary outcome.

METHODOLOGY

The study was an open, 8-week period trial conducted to measure the concentration of CRP and to evaluate the effect of captopril and amlodipine on the concentration of CRP in hypertensive type II diabetic patients who were collected from Al-Waffa Center for Diabetes Management and Research in Mosul. The study protocol was approved by the local research Ethics Committees of the University of Mosul and Mosul Health Administration.

One hundred hypertensive type II diabetic patients participated in the study. They were divided into two groups, each of 50 patients. Group one kept on captopril (SDI Company, Iraq) therapy in doses of 25 to 50mg, two to three times daily. It included 14 males and 36 females, with mean ages of 55.42 ± 7.97 years. Group two was kept on amlodipine (Ajanta Pharma Limited/ India) therapy in doses of 5 to 10 mg as a single daily dose. It included 16 males and 34 females with mean ages of 54.22 ± 6.45 years.

Another fifty apparently healthy individuals, sex and age - matched with the patients also participated in the study as a control group. They were 16 males and 34 females whose ages mean were 53.4 ± 9.15 years.

Inclusion & Exclusion criteria: The inclusion criteria included patients with type II diabetes mellitus newly diagnosed hypertensive patients having blood pressure $\geq 140/90$ mmHg. Exclusion criteria included patients with hepatic or renal diseases, pregnant and lactating women or any other diseases which may have inflammatory reactions and hypertensive patients on antihypertensive therapy.

Blood pressure was measured at baseline (before drug administration) by standard mercury sphygmomanometer and at the end of 8

week treatment period with captopril or amlodipine. Goal blood pressure after treatment was less than 140/90 mmHg. Antihypertensive efficacy was assessed by finding the differences between blood pressure before and after drug therapy and by the determination of the number of patients achieved normal blood pressure after therapy.

Serum CRP was assessed by using Chemelex, S.A. kit (Pol. Ind. Can Castells. C/ industria 113.Nau J) before and after drug administration. The upper range of normal serum CRP level was considered up to 6mg/L. CRP were also measured in the control subjects.

All values were quoted as the mean \pm SD. Paired t-test was used to compare blood pressure and serum CRP concentrations at baseline and after treatment, unpaired t-test was used to compare between the reduction of CRP by captopril and amlodipine. Paired t-test was used to compare between serum CRP concentration of the control group with those of the patients. Level of significance was considered significant at $P \leq 0.05$.

RESULTS

Table-I shows blood pressure of the patients in the captopril and amlodipine groups before and after therapy. A significant reduction of BP were obtained in both groups after therapy with captopril or amlodipine. The percentage of patients achieved normal blood pressure were 70% for captopril group and 66% for amlodipine group. No significant differences

Table-I: Blood Pressure of Captopril and Amlodipine Groups Before and After Therapy (mmHg).

Drug	Parameter	Mean \pm SD	P value
Captopril	Before	159.94 \pm 11.1/ 102.7 \pm 9.8	<0.001
	After	130.56 \pm 9.65/ 80.1 \pm 7.86	
Amlodipine	Before	163.46 \pm 13.37/ 105.9 \pm 11.19	<0.001
	After	132.7 \pm 10.56/ 81.8 \pm 8.25	

in the reduction of BP were obtained between the two groups ($P > 0.5$) (Table-II).

A significant reduction of serum CRP level was demonstrated after treatment with captopril ($P < 0.005$) (Table-III). No significant reduction of CRP was demonstrated after therapy with amlodipine (Table-IV).

Mean CRP concentration of the control group was 2.16 \pm 2.91mg/L which is statistically lower than values of 12.12 \pm 9.81mg/L and 12.6 \pm 9.49 of captopril and amlodipine groups, respectively ($P < 0.001$). Comparison between the reduction of CRP concentrations after therapy with captopril (4.92 \pm 11.29) and amlodipine (0.12 \pm 12.1) shows a significant difference ($P < 0.025$).

DISCUSSION

The data obtained from the present study showed that both captopril and amlodipine are effective antihypertensive drugs and achieved the therapeutic goal in a higher proportion of patients. These results are in agreement with the results obtained from previous studies that also demonstrates that captopril and amlodipine are effective antihypertensive drugs.²⁴⁻²⁷ The present study demonstrated that the hypertensive, type II diabetic patients are associated with higher level of serum CRP concentrations compared with the healthy individuals this may suggests the presence of an inflammatory state in such patients as represented by elevated serum CRP concentrations, an important marker of inflammation. An 8-week treatment with captopril resulted in changes toward a significantly lower level of serum CRP compared with amlodipine.

Elevation of serum CRP was demonstrated in many diseases including, myocardial infarction, angina, stroke, diabetes mellitus,

Table-II: Reduction of Blood Pressure in The Captopril and Amlodipine Groups after Therapy (mmHg).

Parameter	Captopril	Amlodipine	P value
Systolic	29.38 \pm 15.92	30.76 \pm 15.14	>0.5
Diastolic	22.6 \pm 13.1	24.1 \pm 14.66	>0.5

Table-III: Serum CRP Concentration Before and After Treatment with Captopril

Parameter	n Patients	Before Treatment	After Treatment	P value
CRP Concentration mg/L	50	Range: 0-24 Mean 12.12± 9.81	Range: 0-24 Mean: 7.2± 8.9	P<0.005

metabolic syndrome, hypertension and atherosclerosis suggesting that inflammatory process may precipitate in the pathogenesis of these diseases.²⁸ Recent research has focused on the use of CRP a marker of inflammation, in the detection of patients at increased risk for cardiovascular disease²⁸ and the addition of CRP to current strategies for global risk assessment, such as the Framingham Risk Score, may have the potential to increase the accuracy of cardiovascular risk prediction.²⁹⁻³¹ Thus the findings in the present study may be of clinical importance as CRP is thought to be independent risk factor for cardiovascular disease.³²

In addition to captopril which is reported in the present study to reduce the concentration of CRP in hypertensive diabetic patients, a number of other agents have been reported by other studies to reduce the concentration of CRP in another disease. Reduction in CRP levels have been seen following treatment with statins a group of hypolipidemic agents including pravastatin, simvastatin, and atorvastatin.³³ In addition many other drugs have been found to affect the concentration of CRP including azetimibe,³⁴ aspirin and clopidogrel³⁵ and the antihypertensive drug valsartan.³⁶

Review of literature demonstrated that the angiotensin-converting enzyme (ACE) inhibitor ramipril reduce serum CRP concentrations in few trials.^{37,38} In contrast to these studies quinapril an angiotensin converting enzyme inhibitor was found to have no effect on serum CRP concentrations,³⁹ also nifedipine a calcium channel blocker was found to produce no change on serum CRP concentrations.⁴⁰

Angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists are recommended for treating hypertension in patients with type II diabetes mellitus based on the efficacy of these drugs in lowering elevated blood pressure and lack of adverse metabolic effects.⁴¹ In addition as patients with diabetes mellitus, showed an increased concentration of CRP compared with nondiabetic counterparts, and CRP is also higher in hypertensive patients and as captopril was found in the present study to reduce serum CRP concentrations, captopril may be regarded as the drug of choice in the treatment of BP in diabetic hypertensive patients.

The reduction of C-reactive protein concentrations reported in the present study which is an important marker of inflammation may be related to the primary action of captopril, an angiotensin converting enzyme inhibitor which act by reducing the synthesis of angiotensin II from angiotensin I. Recent work has shown that angiotensin II has significant proinflammatory actions in the vascular wall, inducing the production of reactive oxygen species, inflammatory cytokines, and adhesion molecules.⁴²

CONCLUSIONS

The present study showed that hypertensive type II diabetic patients are associated with increased level of CRP and therapy with captopril but not amlodipine significantly reduced CRP, suggesting a possible anti-inflammatory action of captopril in addition to its BP lowering effects. Thus captopril may be regarded as the drug of choice in the treatment of BP in diabetic hypertensive patients.

Table-IV: Serum CRP Concentration Before and After Treatment with Amlodipine.

Parameter	n Patients	Before Treatment	After Treatment	P value
CRP Concentration mg/L	50	Range: 0-24 Mean 12.6± 9.49	Range: 0-24 Mean: 12.48± 9.76	P>0.5

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