Discussion
6.0 DISCUSSION

The present study was carried out to study the interaction of angiotensin converting enzyme inhibitors (ACEIs), enalapril and lisinopril, and concomitantly administered diclofenac sodium in non-diabetic and diabetic hypertensive arthritic patients. Apart from the demographic profile of the patients viz. age, sex, height, weight, risk factors involved and underlying diseases (Table 1), physical parameters like systolic blood pressure (SBP), diastolic blood pressure (DBP) and biochemical parameters viz. insulin sensitivity and urinary albumin excretion rate (in diabetic patients only), platelet aggregation, serum creatinine, blood urea nitrogen (BUN), serum sodium, serum potassium, lipid profile (serum cholesterol, serum triglycerides, serum LDL, serum HDL, serum LDL/HDL ratio and serum cholesterol/HDL ratio), SGOT and SGPT were studied.

In the present study, blood pressure was the only physical parameter studied. Treatment with both enalapril and lisinopril significantly reduced both systolic and diastolic blood pressure in non-diabetic as well as diabetic patients. But, on concomitant treatment with diclofenac sodium, both the ACEIs lost blood pressure control significantly.

Prostaglandins (PGs) play an important role in cardiovascular homeostasis. Among other things, they promote vasodilatation and enhance sodium excretion. Since they act as local hormones, it is difficult to assess their activity in the intact organism. Various reports have stated increase in circulating levels and/or excretion of vasodilator PGs or their metabolites in hypertensive patients during treatment with ACEIs (Fagard et al, 1979; Vinci et al, 1979; Swartz et al, 1980). There are reports of increase in PGE₂ metabolites in plasma after captopril administration in normotensive subjects (Swartz et al, 1980) and in patients with essential hypertension on a low sodium diet (Moore et al, 1981). Silberbauer et al (1982) suggested that PGs are involved in the mechanism of antihypertensive action of captopril.

The relative importance of angiotensin-II (A-II) and kinins in the antihypertensive activity of ACEIs has been debated since ACE has been proven
to be identical to kininase II, one of the kinin-degrading enzymes. Blocking this enzyme inhibited both A-II generation as well as kinin breakdown (Bhoola et al, 1992; Linz et al, 1995). Bradykinin has been reported to release PGs from several tissues (McGiff et al, 1972; Blumberg et al, 1977) and inhibition of kininase II by ACEIs can increase kinin levels, allowing more kinin-related PGs to be released. This issue has an obvious theoretical and practical importance and, probably not only confined to hypertension, but also involves congestive heart failure, which is the other major field of clinical application of ACEIs.

Cleland (1993) stated that the antihypertensive effect of some ACEIs can be interfered with by drugs which block PG synthesis, but where and how, is not fully understood. Occasional uses may not matter, but if aspirin, ibuprofen or indomethacin is used regularly, blood pressure must be monitored. Nonsteroidal antiinflammatory drugs (NSAIDs) block the synthesis of prostaglandins and thus may interfere with circulatory control. Indeed, many reports show that blood pressure may rise during treatment with one of these drugs (Silberbauer et al, 1982; Oparil et al, 1987). However, meta-analyses of such reports indicate that the rise in mean arterial pressure is relatively small, being approximately 5 mm Hg. At this stage, it is not known whether this confers any risk in terms of cardiovascular complications. Moreover, the trials on which this information is based are of relatively short duration. Contrary to this, combination therapy with sulindac (200 mg b.i.d.) or indomethacin (50 mg b.i.d.) with enalapril (20 mg b.i.d.) did not blunt the antihypertensive efficacy of enalapril (Oparil et al, 1987).

It is reported (Guazzi et al, 1998) that in the short-term treatment, 300 mg aspirin inhibited the antihypertensive effect of enalapril in not less than 50% of the patients. The authors observed that aspirin selectively antagonised the antihypertensive effect of enalapril, but not that of combination of nifedipine and atenolol; and this antagonistic effect occurred more in patients with severe hypertension (91% inhibition of the antihypertensive effect of enalapril) than in patients having mild to moderate hypertension (63% inhibition of the antihypertensive effect of enalapril). However, incidences of antagonism in mild to moderate hypertension was similar to one in the severe form, suggesting that
the severity of hypertension is not a major determinant of the occurrence of counteraction of NSAIDs to the effects of ACEIs (Guazzi et al, 1998). These observations are of practical importance because the incidence of counteraction with a dose within therapeutic range appears to be the same as that reported with much greater (eight times) doses of aspirin used by Moore et al (1981) for probing PG blockade during ACE inhibition. Blunting of the antihypertensive effect of enalapril by aspirin suggests a PG participation in the antihypertensive efficacy of enalapril.

The attenuation of the antihypertensive effect of enalapril and lisinopril by diclofenac sodium observed in our study is also in agreement with the report of Joint National Committee (1993) which states that NSAIDs (including aspirin and ibuprofen) may offset blood pressure control by ACEIs through inhibition of PG synthesis and that ACEIs increase PG synthesis. The beneficial effect of aspirin in coronary artery disease (CAD) is through PG inhibitory activity (The Persantine-Aspirin Reinfarction Study Research Group, 1980; Antiplatelet Trialists' Collaboration, 1988). In our opinion, this PG inhibition may produce complications when aspirin is administered in higher doses, as in case of arthritis. Therefore, due monitoring of blood pressure may be indicated during combined administration of NSAID and ACEI. However, no attempt has been made in the present study to find interaction of ACEI and NSAIDs in patients receiving low doses of NSAIDs. e.g. patients of CAD.

In the present study, insulin sensitivity was measured as glucose disposal rate, $K_{\text{ITT}}$, by the method of Appa Rao & Snehalatha (1996). Insulin sensitivity was significantly enhanced in patients receiving chronic treatment with enalapril or lisinopril. Combining diclofenac sodium with enalapril or lisinopril counteracted the enhancement of insulin sensitivity shown by any of the two ACEIs, i.e. we observed significant lowering of insulin sensitivity in diabetic patients receiving diclofenac sodium-ACEI combination when compared with the patients receiving ACEI alone. Therefore, it is suggested from our study that patients with diabetes, hypertension and arthritis receiving long-term treatment with oral hypoglycaemics, ACEI and diclofenac sodium must be closely monitored for dose adjustments to maintain an optimal glycaemic control.
Insulin resistance with consequent hyperinsulinaemia, glucose intolerance and dyslipidaemia, all metabolic changes that represent independent risk factors for coronary heart disease, are more common in hypertensive patients than the normotensive ones (Modan et al, 1985; Stout, 1985; Ferrannini et al, 1987; Fuh et al, 1987; Shen et al, 1988; Ferrannini et al, 1989; Ferrannini et al, 1990; Pollare et al, 1990; Natali et al, 1991). In patients of NIDDM, hyperglycaemia leading to poor glycaemic control, hyperinsulinaemia, hypertension, dyslipidaemia and possibly other conditions are believed to be linked to insulin resistance as part of the cluster of conditions known as 'Syndrome X' (Goa et al, 1997).

Enhancement of insulin sensitivity by ACEIs has also been demonstrated by Bönner (1997) using glucose clamp technique. Further, Paolisso et al (1992) compared the antihypertensive efficacy and the effects on insulin sensitivity of 5 different ACEIs viz captopril, enalapril, quinapril, ramipril and lisinopril, and of placebo. Lisinopril displayed a statistically significant greater improvement in insulin sensitivity than other ACEIs. It was interesting to note that the improvement in insulin sensitivity was paralleled by a decline in plasma triglycerides and free fatty acids.

The proposed mechanism behind the beneficial effects of ACEIs on metabolism is an improvement in transport of glucose and insulin to skeletal muscle. Vasodilatation increases blood flow through the muscle leading to enhanced glucose utilization (Berne et al, 1991). Other possible mechanisms may include improved insulin release from pancreas and accumulation of vasodilator bradykinin (Cziraky et al, 1996).

In our study, urinary albumin excretion has been reduced following chronic treatment with enalapril and lisinopril in diabetic patients. Whereas urinary albumin excretion increased in diabetic, hypertensive and arthritic patients receiving oral hypoglycaemics along with ACEI and diclofenac sodium when compared with nonarthritic diabetic hypertensive patients receiving oral hypoglycaemics and ACEI but not diclofenac sodium. The findings of our study reveal that urinary albumin excretion rate (AER) is increased following
treatment with diclofenac sodium and enalapril or lisinopril combination. This shows ability of diclofenac sodium to attenuate the antiproteinuric effect of the two ACEIs under study in diabetic hypertensive and arthritic patients. This finding is contradictory to the reports of additive antiproteinuric effect of NSAID and ACEI combination (Heeg et al, 1990; 1991). However, our findings confirm the beneficial effects of ACEIs in diabetic hypertensive patients as evident from reduction in urinary albumin excretion rate. Further, the findings of our study advocate due monitoring of urinary albumin excretion rate in those patients who are receiving chronic treatment with ACEIs and diclofenac sodium simultaneously.

ACEIs have been reported to reduce proteinuria and progression of nephropathy in type II diabetes mellitus. They have been shown to reduce urinary albumin excretion and also to reduce the instance of overt nephropathy in both IDDM (Feman et al, 1993; Sowers & Epstein, 1995) and NIDDM (Sawicki et al, 1991; Cziraky et al, 1996) patients. Therefore ACEIs are recommended as the drugs of choice for treating hypertension associated with diabetic nephropathy as they reduce proteinuria and slow down progression of renal disease (Mogensen, 1992). Further, Baba et al (1997) have reported antiproteinuric effect of ACEIs in hypertensive NIDDM patients with established nephropathy.

On the basis of a meta-regression analyses (Kasiske et al, 1993), it has been reported that ACEIs decrease proteinuria and preserve glomerular filtration rate (GFR) in patients with diabetes mellitus. It has also been suggested that the effects of ACEIs are independent of changes in systemic blood pressure, suggesting a unique renoprotective effect of agents of this class. Bianchi et al (1991, 1992) and Bigazzi et al (1993) have observed in short and long term studies, the effects of ACEIs in patients with arterial hypertension (maintained renal function and urinary protein excretion between 30 and 200 mg/24h). The authors found that enalapril significantly decreased the protein excretion rate.

Several reports have stated that the aspirin like drugs reduce the renal blood flow and glomerular filtration rate in the patients with congestive heart failure,
hepatic cirrhosis with ascites, or chronic renal disease or in those who are hypovolemic for any reason (Clive & Stoff, 1984; Patrono & Dunn, 1987; Oates et al, 1988); acute renal failure may be precipitated under these conditions. In all of these settings, renal perfusion is more dependent upon PGs that cause vasodilatation and that can oppose the vasoconstrictive influences of norepinephrine and A-II resulting from the activation of pressor reflexes (Insel, 1996). However, this vasoconstrictor effect will lead to renal damage in the clinical settings mentioned above because of the inhibition of the formation of vasodilator PGs by aspirin-like drugs.

In the present study, we have estimated percent platelet aggregation in an attempt to find the effect of ACEIs on platelet aggregation and how it is affected by co-administration of diclofenac sodium. There was no significant alteration in percent platelet aggregation in the patients receiving chronic enalapril or lisinopril treatment when compared with the values of their respective pre-treatment (or post-washout) stage. However, percent platelet aggregation was significantly reduced in the patients receiving enalapril or lisinopril along with diclofenac sodium when compared with those receiving enalapril or lisinopril alone.

Human platelets possess specific A-II receptors and A-II increases intracellular Ca" in platelets through transmembrane ion flux (Lonn et al, 1994). Physiological concentration of A-II increases platelet aggregatory response and decreases the stimulatory threshold of agonists such as adrenaline and adenosine (Lonn et al, 1994). ACEIs possess antithrombotic property the mechanism of which appears to be platelet inhibition (Remme, 1997). A-II stimulated platelets are more sensitive to aggregatory factors such as collagen or epinephrine, and therefore ACE inhibition may reduce platelet aggregation (Swartz & Moore, 1990; Someya et al, 1984). It is reported that in platelets obtained from patients with myocardial infarction and congestive heart failure (NYHA class III to IV) and who were given lisinopril for 3 months, time to ADP-induced aggregation lengthened by 40 to 170% versus baseline (Pasechnic et al, 1995). Platelet activity was not influenced in those patients of hypertension who received lisinopril 20 mg/day for 4 weeks (Zannad et al, 1993). However,
erythrocyte aggregation time was prolonged by lisinopril and whole blood viscosity tended to decrease in these patients. In an experimental model, Pawlak et al (1998) observed that ACEIs possess antithrombotic property and that nitric oxide and PGI\(_2\) are involved in this activity.

NSAIDs have been reported (Luscher & Weber, 1993) to inhibit platelet aggregation in low doses. Though only aspirin among the NSAIDs has been used in clinical practice for conditions requiring reduction in platelet aggregation, other agents may also possess this property.

Our study suggests that patients with arthritis and hypertension with or without diabetes mellitus may benefit from concomitant use of ACEIs and diclofenac sodium so far as antiplatelet activity is concerned. Therefore, this combination may additionally be beneficial in checking cardiovascular complications. The inter-connection between fibrinolysis/haemostasis, hypertension and coronary artery disease is complex and incompletely understood; however, agents which normalise platelet activity and help in maintaining haemostasis can assist in the treatment of these conditions.

In the present study, serum sodium level decreased, although not statistically significant, in the diabetic/non-diabetic patients receiving chronic enalapril and lisinopril treatment. Reduction in serum sodium level was found to be significant in the patients receiving combination of diclofenac sodium with enalapril/lisinopril. However, none of the patients in the study developed any sign of hyponatremia like anorexia, nausea, lethargy, apathy, disorientation, agitation, seizures or depressed reflexes.

Hyperglycaemia and hyperinsulinaemia directly affect renal tubule leading to inhibition of sodium excretion (Kumar et al, 1988), and there is also an increase in activity of the renin-angiotensin-aldosterone pathway, which further exacerbates sodium retention (Tuck et al, 1990). On the other hand, acute natriuresis occurs soon after initiation of ACEI therapy and the new sodium balance is maintained during prolonged treatment with ACEIs (Hodsman et al, 1984). Besides, ACEIs like captopril, lisinopril and enalapril are reported to cause severe hyponatremia (Al-Mufti & Arieff, 1985; Subramanian & Ayus, 1985).
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1992; Gonzalez-Martinez et al, 1993). An early effect of the onset of the enalapril therapy is natriuresis that is related to a modest increase in the fractional excretion of sodium (Leary et al, 1984; McNabb et al, 1985; Sanchez et al, 1985). Some of these authors have related this natriuresis to the inhibition of aldosterone; others noting that plasma aldosterone concentration returned to baseline level soon after starting enalapril therapy, hypothesised that A-II may play a direct role in the tubular excretion of sodium.

NSAIDs have been reported to increase tubular reabsorption of Na⁺, Cl⁻ and water (Clive & Stoff, 1984). They promote the retention of salt and water by reducing the PG-induced inhibition of both. Water retention may also be mediated by increased osmotic pressure due to sodium retention, which stimulates hypothalamic osmoreceptors resulting in increase in antidiuretic hormone (ADH) from posterior pituitary causing retention of water. Here, perhaps retention of water is more, beyond isoosmotic level causing dilutional hyponatraemia. Fluid retention is the most common NSAID-related renal complication, occurring to some degree in virtually all exposed individuals and is readily reversible on discontinuation of the NSAID (Whelton & Hamilton, 1991). This may cause edema in some patients who are treated with an aspirin-like drug. Phenylbutazone causes significant retention of Na⁺ and Cl⁻ accompanied by a reduction in urine volume. This may cause edema. Plasma volume frequently increases by as much as 50% and, as a result, cardiac decompensation and acute pulmonary edema have occurred in patients given phenylbutazone (Insel, 1996).

Prostaglandins favour natriuresis and modulate antidiuretic hormone release (Norris, 1990) and their inhibition by NSAIDs may account for salt retention, edema, reduction in the antihypertensive effect of diuretics and water conservation (Toto, 1991; Shield, 1993). Such adverse effects can be observed virtually with all NSAIDs (Skeith et al, 1994).

In our study, serum sodium levels were significantly reduced in the patients receiving diclofenac sodium in addition to ACEI. Although these observations are not clinically significant as values of serum sodium level were falling within
the normal range, one cannot rule out hyponatraemic effect in the group of patients receiving long-term therapy with diclofenac sodium and ACEIs. The reason for the patients remaining asymptomatic for hyponatraemia despite reduction in serum sodium level could be attributed to the hyponatremia being dilutional one, which is caused because of fluid retention. Therefore, these patients should be closely observed for any clinical symptoms of hyponatraemia.

In the present study, serum potassium level increased in patients on chronic ACEI (enalapril or lisinopril) therapy when compared with the baseline values and in patients receiving chronic treatment with either of the two ACEIs plus diclofenac sodium in hypertensive patients with or without diabetes mellitus. The level of significance was found to be more with enalapril \((p=0.03; p=0.002)\) than with that of lisinopril \((p=0.04; p=0.09)\) treatment in nondiabetic and diabetic patients respectively. This difference in terms of serum potassium levels may be because of the inherent characteristics of the two ACEIs. However, none of the patients developed any sign of hyperkalemia such as fatigue, weakness, tingling, numbness, paralysis, bradycardia, palpitations, or difficulty in breathing as the values remained in the normal physiological range.

Significant retention of \(K^+\) is rarely encountered in patients with normal renal function who are not taking other drugs that cause \(K^+\) retention, despite some reduction in the concentration of aldosterone (Jackson, 2001). However, ACEIs may cause hyperkalemia in patients with renal insufficiency or in patients taking \(K^+\)-sparring diuretics, \(K^+\)-supplements, \(\beta\)-adrenergic receptor blockers, or NSAIDs (Jackson, 2001). Prolonged treatment with enalapril alone appears to have little or no effect on the fractional excretion of potassium (Bauer, 1984), although sufficient potassium retention occurs to cause a marginal increase in serum potassium concentration (Bauer & Jones, 1984; Webstar et al, 1985). Reversible hyperkalemia has been reported to be caused by lisinopril therapy (Lancaster & Todd, 1988). Hyperkalemia has occasionally been observed during lisinopril therapy in the patients with (Bakris et al, 1996) or without (Zeneca Pharma Inc., 1995; Andrivet et al, 1989) diabetes mellitus. There is also a
report in which eleven percent of patients with diabetes in one trial developed hyperkalemia following lisinopril therapy (Bakris et al, 1996).

ACEIs are known to reduce aldosterone secretion and potassium retention is not uncommon during treatment with such agents (Jackson & Garrison, 1996). NSAIDs are also reported to cause hyperkalaemia (Insel, 1996; Whelton & Hamilton, 1991). Our observations are parallel with the report of Kaplan & Taylor (1992) who observed hyperkalaemia in patients receiving ACE-I and NSAID combination. Thus, it could be suggested that patients must be monitored for serum potassium levels too, to avoid complications that may occur due to hyperkalaemia.

In the present study, serum creatinine as well as BUN levels increased significantly in patients receiving ACEI and diclofenac sodium when compared with those on chronic ACEI treatment alone.

Serum creatinine elevation (> 25 mg/L) is rarely seen in the patients with essential hypertension and normal renal function who are receiving enalapril alone and is comparable with that of control groups (McFate Smith et al, 1984). It is reported that a patient with essential hypertension developed increased serum creatinine (37 mg/L) with glycosuria after 16 week treatment with enalapril 20 mg twice daily and hydrochlorothiazide 50 mg twice daily, but this was resolved after discontinuation of enalapril therapy (Cressman et al, 1982). In a randomized double-blind placebo-controlled study, enalapril was reported to increase serum creatinine levels in the patients of CHF (Kjeksus & Swedberg, 1989).

It is reported (Anderson et al, 1986; Mayer et al, 1990; Morelli et al, 1990) that ACEIs have a protective effect against the progression of renal insufficiency following renal injury. However, many reports suggest that ACEIs should be contraindicated in patients with renal artery stenosis (Kaplan & Taylor, 1992). Other investigators have suggested that factors other than glomerular hypertension are important for progression of chronic renal failure. Thus, glomerular hypertrophy rather than glomerular hypertension have been indicted in the disease process (Yoshida et al, 1989; Fisher & Absher, 1995).

It is reported (Whelton & Hamilton, 1991) that fluid retention is the most common NSAID-related renal complication, occurring to some degree in virtually all exposed individuals. Also, as mentioned earlier, several reports have stated that the aspirin like drugs reduce the renal blood flow and glomerular filtration rate in the patients with CHF, hepatic cirrhosis with ascites, or chronic renal disease or in those who are hypovolemic for any reason (Clive & Stoff, 1984; Patrono & Dunn, 1987; Oates et al, 1988); acute renal failure may be precipitated under these conditions. In all of these settings, renal perfusion is more dependent upon PGs that cause vasodilatation and this can oppose the vasoconstrictive influences of norepinephrine and A-II resulting from the activation of pressor reflexes (Insel, 1996). It is now well established that when renal perfusion pressure decreases, pressor reflexes release norepinephrine via sympathetic stimulation and, renn from the juxtaglomerular cells of the islets of Langerhan in the kidneys leading to release of A-I, which finally gets converted to A-II by the ACE. Both norepinephrine and A-II being vasoconstrictors, bring the renal perfusion pressure back to normal (Insel, 1996). However, this vasoconstrictor effect may lead to renal damage in the clinical settings mentioned above because of the inhibition of the formation of vasodilator PGs by aspirin-like drugs.

Although nephropathy is uncommonly associated with the long-term use of individual aspirin-like drugs, the abuse of analgesic mixtures has been linked to the development of renal injury including papillary necrosis and chronic interstitial nephritis (Kincaid-Smith, 1986). Chronic abuse of any aspirin-like drug or analgesic mixture may cause renal injury in susceptible individuals (Maher, 1984). An acute interstitial nephritis can also occur as a rare complication of the use of aspirin-like drugs (Pirson & van Ypersele de Strihou, 1986; Whelton & Hamilton, 1991).

The acute effect of ACEI on renal function is more deleterious than beneficial. Long term result is despite a continuing slight reduction in GFR; renal Na'
retention is reversed without a need for increase in diuretic therapy (Cleland, 1993). It is known that renal function may worsen during therapy with lisinopril, usually in the patients with severe congestive heart failure or renal disease (Zeneca Pharma Inc., 1995). Recently, it has been reported (Bouvy, 2002) in a European Society of Clinical Pharmacy meeting that patients on angiotensin-converting enzyme (ACE) inhibitors are at increased risk of renal dysfunction when they start using non-steroidal anti-inflammatory drugs (NSAIDs).

In the present study, a rise in BUN level shows that GFR and blood flow to the kidneys might be reduced in the patients receiving the concomitant treatment of diclofenac sodium and ACEI. These findings are in agreement with the recent report of Bouvy (2002) mentioning an increased risk of hospitalisation for renal dysfunction at the start of NSAID therapy in users of ACE inhibitors. Increase in serum creatinine and BUN levels in these patients can be attributed to the inhibition of PG synthesis by diclofenac sodium leading to decreased blood flow to the kidneys and consequent reduction in GFR. Maintenance of GFR and urea excretion are dependent, to some extent, on A-II levels (Ball & Robertson, 1985) and diclofenac sodium is reported to impair renal function (Insel, 1996). Therefore, in our study, elevation of serum creatinine and BUN levels may be attributed to the inhibition of A-II formation by enalapril or lisinopril and inhibition of PG synthesis by diclofenac sodium.

In our study, serum cholesterol, serum triglycerides, serum HDL and serum LDL levels remained unaltered in diabetic as well as non-diabetic patients on chronic enalapril therapy. These findings are in agreement with the reports that enalapril is lipid neutral (Kaplan & Taylor, 1992; Gordon et al, 1997). On the other hand, another report (Sasaki & Arakawa, 1989) suggested enalapril to be an effective antihypertensive drug with a favourable effect on the lipid profile. Further, Chan et al (1994) reported that twelve weeks of treatment with enalapril in hypertensive NIDDM patients was associated with greater improvement in glycaemic control and greater reduction in serum apolipoprotein-B concentration. We observed a significant reduction in serum triglyceride in both non-diabetic as well as diabetic patients and reduction in
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LDL levels in diabetic patients along with marked rise in serum HDL levels (non-diabetic $p = 0.04$; diabetic $p = 0.08$) in patients receiving concomitant treatment with enalapril and diclofenac sodium.

In our study, though serum cholesterol, serum HDL and serum LDL levels did not change significantly in non-diabetic patients on chronic lisinopril treatment, serum cholesterol as well as serum triglyceride levels decreased significantly in diabetic patients receiving concomitant treatment with lisinopril and diclofenac sodium whereas reduction in serum cholesterol level in non-diabetic patients receiving similar treatment was marginally significant ($P = 0.08$). Marginal significance may have clinical implications and hence needs to be reported as done by Falkner et al (1995). Further, serum HDL levels increased significantly in both non-diabetic and diabetic patients receiving concomitant treatment with lisinopril and diclofenac sodium. Hasslacher (1996) reported that lisinopril brings about a decrease in serum cholesterol, serum triglycerides and serum LDL while slightly raising serum HDL levels. Falkner et al (1995) reported that during lisinopril treatment, there was a significant reduction in total cholesterol and in low-density lipoprotein-cholesterol. It is reported (Abramowicz, 1995) that ACEIs have no adverse effects on plasma lipid concentrations or on glucose tolerance, and some have been shown to prolong survival in patients with heart failure or left ventricular dysfunction after myocardial infarction. It is also reported that ACEIs can have beneficial metabolic effects with improvements in lipid profile (Sawicki et al, 1991).

In the present study, serum LDL/HDL ratio and serum cholesterol/HDL ratio did not alter significantly with chronic treatment with enalapril or lisinopril in non-diabetic or diabetic hypertensive patients when compared with the respective pre-treatment values. However, these values reduced significantly in both non-diabetic and diabetic patients receiving concomitant treatment with enalapril/lisinopril and diclofenac sodium when compared with the patients on long-term enalapril or lisinopril therapy alone. These findings suggest that the concomitant therapy with diclofenac sodium and ACEI has a beneficial effect on lipid profile and may play an important role in checking the cardiovascular complications in the patients of hypertension, diabetes mellitus and arthritis.
SGOT and SGPT levels remained unaltered following chronic treatment with enalapril/lisinopril. Combination of diclofenac sodium and either of the two ACEIs resulted in higher SGOT and SGPT levels in both non-diabetic and diabetic patients as compared to those on the respective chronic treatment with the ACEIs alone. The rise in SGOT levels in the diabetic patients was found to be statistically significant.

Rarely, hepatotoxicity is reported to occur during therapy with lisinopril (Larrey et al., 1990; Hilburn et al., 1993; Droste & de Vries, 1995) and other ACEIs (Hagley et al., 1993). It has been reported with the use of captopril, enalapril and lisinopril. Apparent crossreactivity has also been reported. Potential mechanisms of injury include idiopathic hypersensitivity and modulation of eicosanoid metabolism by inhibition of kininase II and subsequent increased bradykinin activity by ACEIs. Mediation via altered eicosanoid metabolism provides a plausible explanation for crossreactivity among ACEIs. Hepatotoxicity resolves if ACEIs are stopped but may progress to liver failure if treatment is continued (Hagley et al., 1993).

In our study, the reason for unaltered SGOT and SGPT levels in the patients receiving chronic enalapril or lisinopril is difficult to assign. It is reported that aminotransferase levels increase in 15% patients taking diclofenac sodium chronically (Insel, 1996). The reason for the present findings on SGOT and SGPT levels in the patients receiving diclofenac sodium and enalapril or lisinopril in the present study is again difficult to explain, but this may be at least partly attributed to the counteraction of NSAIDs and ACEIs on PG synthesis. Periodic monitoring of hepatic function in the diabetic patients on diclofenac sodium along with either of the two ACEI may help in deciding continuation of the treatment.

It can be suggested from our study that chronic co-administration of diclofenac sodium with ACEIs like enalapril or lisinopril significantly reduced the antihypertensive efficacy of the ACEIs. Besides, insulin sensitivity, serum triglycerides, serum LDL/HDL ratio, serum cholesterol/HDL ratio, serum sodium level, and % platelet aggregation are significantly reduced with chronic
co-administration of diclofenac sodium with the ACEIs. Contrary to this, urinary albumin excretion rate, serum potassium level, serum HDL level, serum creatinine and BUN levels were significantly increased in the patients on concomitant chronic treatment with diclofenac sodium with the ACEIs. Additionally, serum cholesterol level was significantly reduced in diabetic patients on concomitant treatment with lisinopril and diclofenac sodium & serum LDL level was significantly reduced in diabetic patients on concomitant treatment with enalapril and diclofenac sodium.

Further, from the study of Moore et al (1981), it was not clear which PG was involved in the mechanism of antihypertensive effect of captopril, since aspirin inhibits both PGE$_2$ as well as PGI$_2$ production. From our study, it can be speculated that both PGE$_2$ and PGI$_2$ are involved in the mechanism of action of ACEIs since diclofenac sodium attenuated the antihypertensive effect of the two ACEIs where PGE$_2$ is involved and the two ACEIs inhibit platelet aggregation which is mediated through the inhibition of PGI$_2$. Though Bouvy (2002) recommended that NSAIDs should be avoided in people who use ACE inhibitors, we suggest that the prescribing physician should decide whether to add diclofenac sodium to regimen of either enalapril or lisinopril considering the risks and benefits and even if diclofenac sodium is added, due monitoring of the parameters may prevent the deleterious effect of the combination.