3.1 PATHOPHYSIOLOGY OF HYPERTENSION IN DIABETES

3.1.1 PREVALENCE AND EPIDEMIOLOGY:

Arterial hypertension is common in both IDDM and NIDDM. There are, however, substantial differences in the etiology and natural history of hypertension between IDDM and NIDDM (Table: 3.1.1). The exact incidence of hypertension in the diabetic population is difficult to determine because of the confounding factors such as type of diabetes, age, weight, metabolic control, and heredity.

Several studies have attempted to assess the prevalence of hypertension in patients with diabetes-mellitus compared with non-diabetic subjects. However, the methodological problems have often made the interpretation of the results difficult. The older studies suffer from poor experimental design or lack of appropriate controls, and the confounding variables mentioned above were not mentioned in the analysis. Unlike IDDM, where the relationship between diabetes and hypertension indicates the existence of established nephropathy, the prevalence and etiology of hypertension in NIDDM has been more difficult to characterise (Drury 1983). While not all studies have shown an association between hypertension and diabetes (Kenn et al. 1965), the balance of the evidence points to a greater than chance association (Pell & D’Alonzo 1967; Garcia et al. 1974; Barrett-Connor et al. 1981; Vaishnava & Bhasin 1969). Pell and D’Alonzo (1967) found 54% greater prevalence of hypertension in diabetic patients than in an age, sex, and weight matched control population. In the Framingham study, increase in arterial pressure in diabetics was also found with a higher level of incidences in the females (Garcia et al. 1974). By contrast, in the Bedford survey (Jerrett et al. 1982) and the Whitehall study of London male civil servants (Fuller et al. 1983), systolic BP was higher in newly diagnosed and borderline diabetic subjects, but not in
previously diagnosed, diabetic subjects. The Diabetes Intervention study also confirmed an excess of hypertension in newly diagnosed NIDDM (Panzaram 1987).

Table: 3.1.1
COMPARISON OF FACTORS RELATED TO HYPERTENSION IN IDDM AND NIDDM.

<table>
<thead>
<tr>
<th>Excahangeble sodium</th>
<th>Insulin dependent diabetes mellitus</th>
<th>Non-insulin dependent diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>plasma renin activity (Angiotensin-II)</td>
<td>increased</td>
<td>increased</td>
</tr>
<tr>
<td>Plasma renin activity (Angiotensin-II)</td>
<td>decreased</td>
<td>normal/± decreased</td>
</tr>
<tr>
<td>Inactive renin</td>
<td>high with microvascular disease</td>
<td>normal</td>
</tr>
<tr>
<td>Plasma norepinephrine</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>Vascular response to norepinephrine and angiotensin-II</td>
<td>increased</td>
<td>increased</td>
</tr>
<tr>
<td>Insulin level</td>
<td>decreased (possibly increased with insulin therapy)</td>
<td>increased</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>normal/increased</td>
<td>increased</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>35%</td>
<td>10-35% (unknown)</td>
</tr>
<tr>
<td>Family history of essential hypertension</td>
<td>common</td>
<td>common</td>
</tr>
<tr>
<td>RBC Li/Na countertransport</td>
<td>increased</td>
<td>normal</td>
</tr>
<tr>
<td>Hypertension preceeding diabetes</td>
<td>rare</td>
<td>common</td>
</tr>
<tr>
<td>Obesity</td>
<td>rare</td>
<td>common (=85%)</td>
</tr>
<tr>
<td>Improved blood pressure with better diabetic control</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

Confirmation of a true association between hypertension and diabetes is supported by observations made in differing populations. In a report from India, the prevalence of hypertension in 1662 diabetic subjects was over three times greater than that of age and sex-matched non-diabetic control (Vaishnava & Bhasin 1969). Obesity, was reported to be more common in the hypertensive compared to normotensive diabetic subjects. Similar rate of prevalence of hypertension has been shown in USA in diabetic patients aged
20-44 years (Horan 1985), but in the patients of an elder age group (>65 years), this rate was approximately 50% higher.

Further information on the frequency of hypertension in several diabetic populations has come from the World Health Organisation Multinational study of Vascular Disease in Diabetics (Diabetes Drafting Group 1985). In this study 34% of the diabetics were found hypertensive with the proportion being greater in women (36%) than men (31%). A study from the UK (Turner 1985) has shown that up to 40% of the males and 53% of females with diabetes-mellitus had hypertension. Additional studies from United States have shown the prevalence of hypertension to be 56.8% in women and 33.9% in men with an overall crude prevalence of 42% (Sprafka et al. 1988). The population based study of diabetic retinopathy (Klein et al. 1985) showed that hypertension was present in 21.9% of the younger (IDDM) and 58.1% of the older (NIDDM) diabetic subjects. In East Finland, where nearly two third of the population is hypertensive, 60.6% of the males and 64.1% of the females were hypertensive in diabetics, while for the non-diabetic age-matched controls the respective figures were 31.5% and 42.0%.

The patients with NIDDM, in contrast to IDDM, is frequently hypertensive at diagnosis. Nearly one third of subjects with NIDDM are hypertensive at the time of diagnosis of their diabetes mellitus (Vasiitupa et al. 1985; Gottlieb 1974; Pell & D’Alonzo 1967; Barrett-Conoor et al. 1981). Approximately 60% of NIDDM patients more than 60 years of age are hypertensive as compared to 25-30% of the non-diabetic population (Christlieb 1982). In general, hypertension is commonly seen in association with NIDDM, occurring with a frequency of between 30-58% within the diabetic population.

3.1.2 PATHOPHYSIOLOGY:

Despite the importance of hypertension in diabetes mellitus, the pathophysiology of diabetic-hypertension
remains poorly understood. First, there have been quite a limited studies in their focus, and no unifying concepts have emerged to allow a comprehensive understanding of the pathogenesis of hypertension, particularly in type II diabetes. Secondly, much of the animal data related to diabetic hypertension comes from studies in the streptozotocin diabetic rats, where hypertension may be artifactual (Sowers et al. 1988).

3.1.2.1 Sodium Retention and Volume Expansion:

The increased prevalence of hypertension in the diabetic state has been associated with two general abnormalities: Expansion of extracellular fluid volume and increased peripheral vascular resistance (Sowers & Tuck 1981). The observation that exchangeable sodium is increased by 10% in diabetic patients suggests that excessive sodium retention and expansion of extracellular fluid volume may contribute to hypertension in diabetes (Brennan et al. 1979; O’Hare et al. 1985; Weidmann et al. 1979; 1985). This relationship between hypertension and volume expansion is controversial, because increased exchangeable sodium also has been described in normotensive diabetic subjects (Brennan et al. 1979; O’Hare et al. 1985; Weidmann et al. 1979; 1985).

The mechanism of sodium retention is not well understood, but early renal defect and altered distribution of extracellular fluid volume partially may explain this phenomenon (O’Hare et al. 1985; Weidmann et al. 1985). Extracellular fluid volume may be expanded in poorly controlled diabetic patients (Christlieb et al. 1981). Ortola et al. (1987) reported that increased sodium reabsorption results from hyperglycemia-induced chronic volume expansion. Hyperinsulinaemia, which is the characteristic of many NIDDM subjects, could partially account for volume expansion through the known property of insulin to enhance renal tubular sodium reabsorption (DeFronzo 1981). Regardless of the mechanism, volume
expansion is likely to be less important than enhanced vascular reactivity in the pathogenesis of hypertension associated with diabetes.

3.1.2.2 Blood Pressure Regulating Systems:

Various blood pressure regulating systems, including renin-angiotensin aldosterone system (RAS) and the sympathetic nervous system (SNS), have been studied relatively well with respect to diabetes and hypertension (Sowers & Tuck 1981). Low plasma renin activity (PRA) may increase the total body sodium and extracellular fluid volume in diabetic humans (Christlieb et al. 1976; Dechatel et al. 1977). PRA and aldosterone levels are low in the presence of diabetic nephropathy (Brenann et al. 1979; Sowers & Tuck 1981). Christlieb et al. (1976) reported that the renin activity in hypertensive diabetics was lower than those in normotensive diabetics. They also reported suppression of PRA in the acutely diabetic alloxan-treated rat, suggesting that PRA can be low in diabetic models even in the absence of the diabetic nephropathy. DeChatel et al. (1977) also reported a tendency toward reduced renin levels, in hypertensive diabetic patients.

3.1.2.3 Prostaglandins:

Katayama and Lee (1985) examined the role of prostaglandins in mediating the reduced levels of renin. They postulated that relative insulin deficiency in streptozotocin-induced diabetes model results in both a diminished basal renin secretion and a reduced renin release in response to decreased PGE\textsubscript{2} synthesis. Moreover, structural alterations in the afferent renal arterioles and the juxtaglomerular apparatus may account, in part, for the decreased secretion of active renin in some diabetic subjects (Sowers & Tuck 1981). It has been reported that factors which inhibit renin secretion are associated with increased intracellular calcium levels in juxtaglomerular cells (Fray et al. 1987).
3.1.2.4 Catecholamines:

Plasma catecholamine levels generally are normal in metabolically stable nonazotemic diabetic patients with normal or high blood pressure (Sowers & Tuck 1981; Weidmann et al. 1985). In contrast, in diabetic patients with peripheral neuropathy, plasma norepinephrine levels are low and in some poorly controlled diabetic patients, the levels are elevated (Sowers & Tuck 1981). The cardiovascular pressor responsiveness to norepinephrine, however, often is exaggerated relative to plasma concentrations, regardless of sex or age of the patient, modality of diabetic therapy, existence of retinopathy or peripheral neuropathy or blood pressure status (Weidmann et al. 1985). Similarly, pressor responsiveness to angiotensin-II often is increased relative to plasma renin levels (Sowers & Tuck 1981; Weidmann et al. 1985).

3.1.2.5 Vascular Reactivity:

Increased vascular reactivity is seen in both IDDM and NIDDM and in normotensive as well as hypertensive individual associated with diabetes, which suggests an early abnormality in the vascular in diabetes.

Hyperreactivity to both norepinephrine and angiotensin-II at the normotensive uncomplicated stage of diabetes mellitus (Weidmann et al. 1985; Drury et al. 1983) may indicate that this is an important mechanism in the development of hypertension.

3.1.2.6 Baroreceptor Disturbances:

Multiple disturbances in arterial baroreceptors sensitivity have been reported in normotensive subjects with IDDM (Eckberg et al. 1986). The autonomic responses over a range of pharmacologically induced arterial pressure changes was evaluated in 10 young diabetic subjects without autonomic neuropathy and in 12 age-matched non-diabetic control. Subnormal baseline norepinephrine levels and supranormal pressor responses to phenylephrine infusions were observed as sympathetic abnormalities in diabetic
subjects. Parasympathetic abnormalities included subnormal baseline standard durations of R-R intervals and subnormal R-R intervals prolongation during elevations of arterial pressure. These data suggest that disturbances in high pressure baroreceptor function could play an important role in the pathogenesis of hypertension. Comparable studies in NIDDM or in hypertensive diabetic patients of either type, is yet to be performed.

3.1.2.7 Body Fat:
Obese subjects display adaptive changes in sodium metabolism and vascular haemodynamics comparable to those in diabetes. A causal relationship between salt and blood pressure in obesity has been proposed. A low sodium diet with normal calorie counts can decrease blood pressure in obese hypertensive subjects (Dahl et al. 1958), sodium sensitive blood pressure responses are found in obese adolescents (Rocchini et al. 1989). Salt-sensitive blood pressure in obesity may be secondary to increased cardiac output and plasma volume, and the degree to which blood pressure responds to salt is directly correlated with insulin levels (Rocchini et al. 1989). However, studies examining the mechanisms of the hypotensive effect of weight loss show that blood pressure can fall substantially, independent of sodium intake and excretion (Tuck et al. 1981; Reisin et al. 1987).

3.1.2.8 Insulin and Insulin Resistance:
Circulating insulin levels are high in obesity, secondary to resistance to insulin-mediated glucose uptake. Insulin may be a factor in obesity associated hypertension (Lucas et al. 1985). Insulin resistance is also the basic abnormality in NIDDM accompanied by high, normal or low insulin levels, and it may also contribute to the high blood pressure seen in NIDDM. Insulin resistance and increased circulating insulin responses to oral glucose are also found in essential hypertension (Ferrannini & DeFronzo 1989; Reaven 1988). Modan et al. (1985) reported from the Israel
study of Glucose Intolerance Obesity and Hypertension that postglucose insulin levels were higher in hypertensive than in normotensive individuals, even after controlling the body weight. Lithell et al. (1990) found reduced insulin sensitivity (Insulin resistance) in both obese and non-obese essential hypertensive subjects. Thus hypertension per se appears to be associated with hyperinsulinaemia. Additionally, in the normotensive population, insulin correlates with blood pressure (Lithell et al. 1990).

Insulin resistance, with its consequent hyperinsulinaemia, could be one of the mechanisms causing high blood pressure in essential hypertension, obesity and diabetes mellitus (Ferrannini & DeFronzo 1989; Reaven 1988; Lithell et al. 1990). Ferrannini et al. (1987) reported measurements of insulin sensitivity, glucose turnover, and whole body glucose oxidation in a group of young, nonobese, nondiabetic volunteers with untreated essential hypertension. They found that during steady-state euglycemic hyperinsulinaemia, achieved with an insulin clamp technique, total insulin induced glucose uptake was impaired markedly. Virtually all of the defect in overall glucose uptake could be attributed to reduced non-oxidative glucose disposal (glycogen synthesis and glycolysis), suggesting a state of insulin resistance which could be correlated with the severity of the hypertension. Because hypertension is more common with obesity, hyperinsulinaemia could be a common factor in the hypertension associated with obesity as well as that seen in certain diabetic patients. Halkin et al. (1988) also found that Hyperinsulinaemia was associated with elevated erythrocyte sodium, decreased erythrocyte potassium, obesity and hypertension. Indeed, altered membrane cation transport is a characteristic shared in conditions of hypertension, obesity and glucose intolerance associated with hyperinsulinaemia (Christlieb et al. 1985; DeLuise et al. 1980; Mogensen 1979; Mott et al. 1985; Singer et al. 1985; Sowers et al. 1982; 1988a; 1988b).
Hyperinsulinaemia also enhances renal tubular sodium reabsorption, which also could explain volume expansion and increase in total body exchangeable sodium seen in diabetic patients (Brennan et al. 1979; O’Hare et al. 1985; Weidmann et al. 1979; 1985). Thus, hyperinsulinaemia and, perhaps, insulin resistance appear to be the factors in the pathogenesis of hypertension in diabetes as well as in obesity.

In IDDM, insulin resistance is not generally recognized as the major defect. When it occurs, it is usually secondary to insulin antibodies. However, in IDDM there appears to be a defect in insulin response as well as in insulin secretion. Nielsen et al. (1987), using the insulin clamp in IDDM subjects, reported peripheral insulin resistance to glucose uptake. Trevisan et al. (1986), using similar techniques, reported that insulin resistance affects not only the glucose but also to lipid and protein metabolism in IDDM. Thus, decreased insulin-mediated glucose uptake under euglycemic conditions is shared by IDDM and NIDDM patients and could contribute to high blood pressure in both conditions.

There are several reasons why insulin might cause hypertension. It affects the sympathetic nervous system, sodium handling by the kidney and vascular function (Fig.3.1.1).

Fig.3.1.1: Effect of insulin on blood pressure regulatory system.

- **INSULIN EFFECT**
  - **SYMPATHETIC ACTIVITY**
  - **VASCULAR REACTIVITY**
  - **SODIUM RETENTION**
  - **BLOOD PRESSURE**
Insulin infusion using the euglycemic hyperinsulinaemic clamp in normal subjects increases plasma norepinephrine concentration, presumably by a direct effect on a nervous system (Rowe et al. 1981). Insulin infusion in healthy subjects also markedly reduces sodium excretion (DeFronzo 1981), probably by directly enhancing sodium reabsorption in the proximal and distal tubules (DeFronzo 1981; Baum 1987) and by reducing free water clearance (Baum 1987). Insulin directly affect the blood vessels, altering vascular response to catecholamines and angiotensin-II (Yagi et al. 1988). Insulin has mitogenic properties and can potentiate vascular smooth muscle cell growth, which could in turn promote atherosclerosis (Stout 1985; Stolar 1988). Changes in vascular wall structure and diameter also favour increased vascular reactivity and development of hypertension (Folkow 1978).

The etiology of the increased peripheral vascular resistance and enhanced smooth muscle contractility in the diabetic hypertensive state is unclear. A possible role for decreased cellular insulin action in mediating the enhanced vascular reactivity is suggested by a number of observations. For example, insulin treatment normalizes aortic and mesenteric vascular hyper-reactivity in streptozotocin-induced diabetes mellitus in rats (MacLeod 1985; Resh 1985). This observation supports the hypothesis that the exaggerated smooth muscle contractility may be secondary to cellular insulin deficiency and resultant abnormalities in cellular cation transport. Insulin is known to stimulate Na⁺ efflux in muscle tissue and other cells (Resh et al. 1980). This effect is inhibited by cardiac glycosides (Cohen et al. 1985; El-Seilfi et al. 1987; Levy et al. 1986a; Resh 1982), suggesting that insulin modulates the transport activity of the (Na⁺-K⁺)-ATPase pump. The significance of insulin in the activation of this membrane enzyme is evidenced further by the fact that insulinopenic rat models of diabetes are associated with decreased (Na⁺-
K⁺)-ATPase activity (El-Mallakh 1986; El-Shelif et al. 1987; Levy et al. 1986a), although this may not be the case in one noninsulin-dependent rat model (Blaustein & Hamlyn 1984). Reduced (Na⁺-K⁺)-ATPase represents one mechanism that could contribute to higher Ca²⁺ in the diabetic hypertensive state. Reduced pump activity theoretically should cause high sodium. This, in turn, would decrease Na⁺-Ca²⁺ exchange function (Greene 1986; Greene & Latimer 1986), with a resultant increase in intracellular calcium.

In addition to the influence of the Na⁺-Ca²⁺ exchanger on Ca²⁺, calmodulin dependent Ca²⁺-ATPase activity is important for extrusion of Ca²⁺ from the cells (Levy et al. 1986b; 1986c; Pershadshingh & MacDonald 1984). There is a increased intracellular calcium and vascular resistance may result from impaired calcium efflux via this pump. Insulin recently has been shown to modulate membrane Ca²⁺-ATPase activity (Berk et al. 1987; Gupta et al. 1986; Hope-Gill et al. 1979; Hoskins & Scott 1983; Zemel et al. 1987). Correspondingly, alterations in Ca²⁺-ATPase activity have been noted in both streptozocin-induced insulinopenic (Moore 1985) and insulin-resistant (Modan et al. 1985) rats.

Marked defect in Ca-ATPase activity is associated with increased intracellular calcium in erythrocytes of hypertensive type II diabetic patients (Zemel et al. 1987). This defect appears to be a result of diabetes-induced alterations in calmodulin, such as nonenzymatic glycosylation, rather than from an intrinsic diabetes-induced pump defect (Zemel et al. 1988b).

Insulin resistance in a hyperinsulinaemic animal model of obesity is characterised by a generalised defect in calcium metabolism including a significant impairment in membrane Ca-ATPase activity similar to that observed in diabetic humans, and corresponding increase in both intracellular calcium and blood pressure compared with lean control rats (Zemel et al. 1988b). It therefore, appears
that insulin resistance may cause a calcium pump defect, which results in increased intracellular calcium and blood pressure.

It is important to emphasize that increased Ca\(^{2+}\) is the only factor contributing to increased vascular smooth muscle tone in the diabetic hypertensive condition. Decreased Ca\(^{2+}\)-ATPase activity, as observed in the state of cellular insulin deficiency is associated with decreased cellular H\(^+\) influx (Berk et al. 1987). High pH, in turn, can stimulate the basal Ca\(^{2+}\) calmodulin system, thus augmenting basal contraction (Johns et al. 1987) as well as increasing the effects of hormones that enhance smooth muscle contraction by increasing Ca\(^{2+}\) (Charest et al. 1985). These factors in combination may explain some or all of the enhanced pressor effects of angiotensin-II and norepinephrine in the diabetic hypertensive state.

Some studies suggest that type II diabetic hypertensive individuals are salt sensitive (Zemel et al. 1987; 1988a). This salt sensitivity may reflect effects of insulin on salt retention or decreased ability of these generate natriuretic substance such as dopamine, prostaglandins, and/or other renal natriuretic factors. Salt-induced increase in blood pressure could result from salt-induced increases in magnesium and calcium excretion. In a diabetic subjects, a relative magnesium deficiency, caused by increased urinary magnesium loss, also could contribute to decreased Na-K-ATPase and Ca-ATPase activity because magnesium may play a critical role in the functioning of these pumps (Altura & Altura 1984; Zemel & Sowers 1988). Salt-induced increases in calcium excretion also may play a role in enhancing peripheral vascular resistance in the diabetic population because this increased calciuresis may eventuate in increased serum parathyroid hormone levels and, thereby, increase intracellular calcium and vascular resistance (Zemel & Sowers 1988).
3.2 DIABETES MELLITUS:
A COMPLEX SYNDROME

Diabetes mellitus is a grouping of anatomical and chemical disorders resulting from a number of factors in which there is an absolute or relative deficiency of insulin and/or its function. It is a complex syndrome characterised by hyperglycemia.

Various epidemiological studies dangerously reflect the seriousness of this complex syndrome. Retinal capillary damage resulting in edema, new vessel formation and hemorrhage makes blindness 25 times more prevalent in diabetics than in the normal population. Cataract appears earlier in life and seems to progress more rapidly in diabetics than in non-diabetic patients. Chronic renal failure with proteinuria, resulting from glomerular capillary damage secondary to basement membrane thickening is 17 times more prevalent in diabetics. Axonal dwindling and segmental demyelination in the peripheral nerves, associated with increased incidences of motor sensory and autonomic impairments have also been reported in diabetic patients. Because of increased atheroma, in medium and large arteries, diabetics have a two-fold greater risk of coronary artery disease and stroke and 3 to 4 fold greater risk of symptomatic peripheral arterial disease than the normal population. Amputation in gangrene is several times more frequent in diabetics than in nondiabetics. It has been estimated that on the average, the expected life span of diabetics is only two-third that of non-diabetics.

It is thus important to note that diabetes-mellitus should not be considered simply as synonymous with hyperglycemia, since there are many conditions in which there is impaired glucose tolerance which are not generally associated with the same spectrum of complications (National Diabetes Data Group 1979). These include acute stress (infection, surgery, trauma), hyperlipidaemia, other
endocrine disorders. Pancreatic disease and a large number of complex genetic syndromes (Table:3.2.1).

Table:3.2.1
Classification of diabetes-mellitus and other states of glucose intolerance

I. Diabetes Mellitus
   A. Type I or Insulin dependent diabetes-mellitus
   B. Type II or Non-insulin dependent diabetes-mellitus
   C. Other types

II. Secondary Diabetes
   A. Pancreatic disease (chronic pancreatitis, hemochromatosis, pancreatectomy etc.)
   B. Hormonal (cushing’s syndrome, acromegaly, pheochromocytoma)
   C. Drug or chemical induced (chlorothiazide, phenytoin etc.)
   D. Insulin receptor abnormalities (acanthosis, nigricans, lipodystrophy etc.)
   E. Genetic syndromes (ataxia telangiectasia, progeria, laurence Moon-Biedl syndrome, myotonic dystrophy)

III. Impaired glucose tolerance (chemical diabetes)

IV. Gestational diabetes

3.2.1 COMPLICATION OF DIABETES-MELLITUS AND ABNORMAL CELLULAR CALCIUM METABOLISM :

Although the pathogenesis of the diabetes mellitus remains poorly understood, both IDDM and NIDDM predispose the individual to a similar spectrum of complications, including hypertension, macrovascular and microvascular disease, cataracts, cardiomyopathy, neuropathy and premature aging. Various complications appear to develop along a pathway common to both the types of diabetes mellitus. Yet, not all diabetic patients are affected by all these complications to the same degree. The reasons for this marked variability in the clinical manifestations of the
diabetes syndrome is still not known.

Studies with experimentally induced diabetes in animals and the data from clinical studies reveal that abnormal intracellular calcium metabolism involving one or more regulatory mechanisms is one of the common defects in both IDDM and NIDDM. Abnormal intracellular calcium regulation has been described in cardiac muscle (Allo et al. 1991; Russ et al. 1991; Dhalla et al. 1985), aorta (Ohara et al. 1991), mesenteric and coronary arteries (Agarwal & McNeill, 1987), skeletal muscle (Nishida et al. 1992), kidney (Levy et al. 1986a, 1994), liver (Studer & Ganas, 1989), erythrocytes (Zemel et al. 1990), lens (Cowen et al. 1992), and osteoblasts (Levy et al. 1992) of diabetic animals. Altered intracellular calcium metabolism has also been reported in arteries (Maser et al. 1991), platelets (Ishii et al. 1990) and adipocytes (Siegal et al. 1990) of diabetic patients.

Increased intracellular calcium is one of the most common abnormality reported not only in type 1 and type 2 diabetes-mellitus (Studer & Ganas 1989; Zemel et al. 1990; Levy et al. 1989; Resnick et al. 1991) but also in obesity (Levy et al. 1989; Resnick et al. 1991) and essential hypertension (Sowers 1992; Resnick et al. 1991). Evidence suggests that cation concentration-dependent influx of calcium into platelets is increased with the insulin treatment in patients with diabetes-mellitus (Ishii et al. 1991), and that influx of calcium into the smooth muscle cells of coronary, aortic and mesenteric arteries is increased in insulin deficient rats (Agarwal & McNeill 1987). Furthermore, the density of calcium channels is increased in the skeletal muscle of diabetic rats (Lee & Dhalla 1992).

Although changes in calcium homeostasis in IDDM and NIDDM are not same, and intracellular calcium tends to be increased in both conditions, the specific defects in regulatory mechanisms may be different in the two syndromes. These differences have several potential explanations. First
obesity (Escoubet et al. 1987) and diabetes-mellitus (Dhalla et al. 1985) are associated with changes in membrane phospholipid composition and since these changes are different for insulin-dependent and non-insulin-dependent diabetes (Baldini et al. 1989), the different abnormalities in intracellular calcium regulation in the two conditions may be partially explained by their different abnormalities in membrane phospholipid composition. Similarly, because the membrane phospholipid composition is tissue specific, the corresponding defects in intracellular calcium regulation are also likely tissue specific (Levy et al. 1988).

Fig. 3.2.1: Proposed Relationship Between Abnormal Intracellular Calcium Homeostasis and Diabetic Complications in IDDM and NIDDM (Levy et al. 1994).

Second, it is likely that both hyperglycemia and insulin deficiency affect intracellular calcium regulation.
(Ohara et al. 1991; Dhallal et al. 1985; Sowers 1992). Third, since changes in intracellular calcium metabolism may lag behind the induction of hyperglycemia and hypoinsulinemia in experimentally induced diabetes (Studer & Ganau 1989; Dhallala et al. 1985), the abnormalities of regulation observed in different diabetes models may reflect a difference in chronicity of the diabetic condition.

3.2.2 DIABETES, HYPERTENSION, HYPERLIPIDAEMIA AND CARDIAC DYSFUNCTION:

One of the great advances in medical care in this century has been the introduction of Insulin. From the outset it caused a dramatic decline in diabetic deaths from ketoacidosis. However, within about two decades, the predominant cause of death in diabetes became CHD (Report of WHO Study Group 1985). This however, is not the case throughout the world. Countries with a Northern European culture, USA, South Africa, Australia and New Zealand all have remarkably high rates of coronary disease. On the other hand, countries like China, Japan and Rural Africa, coronary disease is rather an unusual condition (Chen et al. 1991; Keys 1975).

There is a correlation between the median cholesterol level in middle-aged men in all of these societies and the risk of CHD. The cholesterol distribution in a country with little coronary disease, the median value of cholesterol is <4mmol/l, and countries with higher coronary disease rates, the cholesterol level in middle-aged men is somewhere between 6.0 and 6.5 mmol/l. It is interesting that in Japan the incidences of CHD are very low even in their diabetic hypertensives or smokers.

Although cholesterol has the major role in determining the overall CHD risk in a population, cholesterol itself has only a small part to play in identifying individuals at risk of high CHD until it reaches high levels. The interaction of other risk factors with cholesterol is critical in determining individual risk. Raised cholesterol with
hypertension produces a much steeper relationship between
cholesterol and the risk for CHD. For smokers with high
blood pressure the relationship is even steeper (Stamler et
al. 1986). The inclusion of diabetes greatly increases the
risk (Kawate et al. 1978).

Hypertension appears to be critically important in
diabetes mellitus, not only because of its increased
prevalence, but also because it accelerates both the
macrovascular and the microvascular complications of
diabetes. Macrovascular disease manifested as CHD,
peripheral vascular disease and cerebrovascular disease, is
the major cause of morbidity and mortality in NIDDM and
accounts for 49-75% of the mortality in these patients
(Panzaram 1987). While most diabetic complications occur in
association with hypertension (Pyoralla & Laakso 1983;
Diabetes drafting group 1985), the absence of hypertension
is the usual finding in the long term survivors of diabetes
(Oakley et al. 1974). As the control of hyperglycemia alone
in diabetes has not reduced the incidence of macrovascular
disease (Pyoralla & Laakso 1983), other risk factors,
including hypertension, may be the important determinants of
long term outcome in these patients. From the 18 years
follow-up in the Framingham study, diabetic subjects with
modest elevations of blood pressure (Systolic BP of 150mmHg)
had an increased risk of cardiovascular disease compared to
subjects without glucose intolerance (Kannel & Kreger 1981).
Co-existent hypertension and NIDDM are associated with 4-5
times the all cause mortality rate of subjects without both
conditions (Panzaram 1987; Pyoralla & Laakso 1983; Fuller
1985; Gottlieb 1974). Incidences of peripheral vascular
disease is greatly increased in diabetes with hypertension
again being an associated factor (Janka et al. 1980). Stroke
occurs 2-6 times more frequently in the diabetic compared to
non-diabetic patients, with a doubling of frequency in the
hypertensive compared to normotensive diabetic population
(Roemboldt et al. 1983).
3.2.2.1 Lipid Disorders in Diabetes:

Disturbed lipid metabolism is common to both types of diabetes which include an increase in circulating triglycerides, and particularly an increase in very low density lipoprotein (VLDL). The low density lipoprotein (LDL) in NIDDM also tends to be increased, whereas, in IDDM LDL is either a little less than, or about the same as in non-diabetic population. High density lipoprotein (HDL) cholesterol, on the other hand, tends to be lower in the NIDDM than in the IDDM in whom it is generally normal or even higher than in the average non-diabetic person (Durrington 1993).

In comparison to matched non-diabetic populations the dominant abnormality in both IDDM and NIDDM is hypertriglyceridemia (Winocour et al. 1989; Winocour & Laker 1990). The prevalence of hypercholesterolaemia (Predominantly increased LDL-cholesterol) is no greater in IDDM and only marginally greater in NIDDM (Winocour & Laker 1990). However, in the United Kingdom this will of course mean that the prevalence of hypercholesterolaemia (>6.5mmol/l) in diabetic clinics is considerable (27% in IDDM, and upto 50% in NIDDM) (Winocour et al. 1989; Winocour & Lakes 1990). Levels of HDL-cholesterol in NIDDM tend to be lower than matched non-diabetic subjects, whereas in IDDM levels are, on the average, equivalent or higher (Winocour & Laker 1990). There is increasing evidence that altered lipoprotein composition is an intrinsic component of both IDDM and NIDDM (Winocour et al. 1986; Joven et al. 1989; Rivellese et al. 1988; Bagdade & Subbaiah 1989a; 1989b).

An increase in circulating non-esterified fatty acids (NEFA) predominantly from adipose tissue is a first step to lipid abnormality occurs in diabetes. Those NEFA, if not removed by other tissues, are taken up by the liver where they incorporated into triglycerides. The important difference between an IDDM and NIDDM is the extent to which the liver also incorporate them into ketonbodies. This
occurs in starvation and in IDDM. Also in IDDM and even more so in NIDDM the NEFA are esterified in triglycerides. The liver secretes this triglycerides in the form of VLDL, hence the hypertriglyceridaemia.

The hypertriglyceridaemia is also contributed by the fact that the major catabolic pathway for triglycerides is via lipoprotein lipase, an enzyme which is expressed on the endothelial surface of adipose tissue, skeletal muscle and cardiac muscle. The enzyme lipoprotein lipase, is insulin-dependent, so that when there is insulin deficiency or insulin resistance, the activity of this enzyme is reduced which leads to catabolic block. The whole process of release of NEFA from the adipose tissue is accelerated by insulin resistance or insulin deficiency because there is another lipase enzyme inside the adipose cell. This is the intracellular lipase, which is responsible for breaking the triglycerides down into glycerol and NEFA. So, the activity of this enzyme goes up in a state of insulin resistance or deficiency, and the whole process of the release of NEFA is accelerated (Durrrington 1989). Insulin itself also has an inhibitory effect on the release of triglycerides from the liver. The state of insulin deficiency or insulin resistance can also reduced plasma triglyceride clearance as a consequence of impaired activity of lipoprotein lipase (Pykeliston et al. 1975). This may further amplify increases in VLDL levels and contribute to altered metabolism of HDL.

Triglycerides by themselves do not directly cause atheroma. However, some studies suggest that a common feature among diabetics, particularly when hypertriglyceridaemia is present, is an increase in their intermediate density lipoprotein (IDL). This is not necessarily be reflected in a total lipid levels. Cholesterol and triglycerides may be unchanged. IDL may build up because it is an intermediate in the conversion of VLDL to LDL and VLDL production is increased in diabetes even when fasting serum triglycerides are not raised. An
increase in IDL is particularly associated with atheroma (Winocour et al. 1992). It is interesting that those patients who have this primary disorders of lipoprotein metabolism get both coronary heart disease and peripheral arterial disease. By contrast, where there is predominantly an increase in LDL cholesterol, as in familial hypercholesterolaemia, coronary heart disease predominates over other forms of vascular pathology such as peripheral artery disease (Durrington 1989).

A variety of interrelated hormonal and metabolic factors have actions that may profoundly influence lipoprotein levels. These factors are displayed in Fig.: 3.2.2 as the "tangled web" of coronary artery disease risk factors, with insulin resistance and hyperinsulinaemia at the centre.

**Fig.: 3.2.2 The Tangled Web of Coronary Risk Factors**

* Genetic traits identified.

Although high blood pressure is a well recognised risk factor for coronary artery disease (CAD) it has been difficult to demonstrate that the treatment of hypertension leads to improved cardiovascular morbidity and mortality (Swales et al. 1989). Similarly there is no evidence that good glycemic control in patients with NIDDM reduces the
development of CAD, a major cause of premature death in this
group (Multi Centre Study 1983). Reaven (1988) proposed that
these findings may be explained if the conditions are seen
in the setting of a syndrome. He proposed that the term
"syndrome X" should be applied to a series of related
variables that are important in the genesis of CAD. These
include insulin resistance, hyperinsulinaemia, abnormal
glucose tolerance, increased plasma VLDL triglycerides,
decreased HDL-cholesterol and hypertension.

Components of syndrome X
* Insulin resistance
* Hyperinsulinaemia
* Glucose intolerance
* Increased VLDL triglyceride
* Decreased HDL cholesterol
* Hypertension

3.2.2.2 Fibrinogen:

Elevated fibrinogen in non-diabetic population has been
shown to be an independent risk factors for stroke
(Wilhelmsen et al. 1984) and coronary heart disease
(Wilhelmsen et al. 1984; Meade et al. 1986). This fibrinogen
related risk of macrovascular disease is further exaggerated
when there is associated hypertension (Stone & Thorp 1985).
Only a few studies in diabetic subjects have described an
association of fibrinogen with microvascular as well as
macrovascular complications (Barnes 1981; Seviour et al.
1986).

The pathophysiological significance of fibrinogen is
related to its involvement in fibrin deposition, platelet
aggregation and adhesion, and blood viscosity (Smith 1986).
Blood viscosity is also an important determinant of total
peripheral resistance and thus of blood pressure (Letcher et
al. 1979; 1981). Increased blood viscosity has also been
observed in diabetes (Barnes 1981), obesity and smoking
(Meade et al. 1986; Smith 1986).
With the strong association of fibrinogen with vascular disease, the raised fibrinogen and associated rheological changes in the diabetic hypertensive could facilitate arterial wall atheroma (Smith 1986). The increased blood viscosity may also be the critical determinant of blood flow in a vessel previously narrowed by atheroma. Treatment of hypertension may not eliminate fibrinogen dependent processes, as the changes in fibrinogen and viscosity with adrenergic blocker therapy are independent of dose and duration of the pharmacological agent used (Letcher et al. 1979). A recent study in treated hypertensive subjects with NIDDM demonstrated that, despite effective blood pressure control, fibrinogen concentrations and blood viscosity were increased as compared to the normotensive control group (Feher et al. 1988).

3.2.2.3 Obesity:

Obesity is often linked to the development of hypertension (Krieger & Landsberg 1988) and the changes in lipid metabolism glucose tolerance and the development of NIDDM (Reaven 1988). It is also associated with a decrease in insulin sensitivity (Pollare et al. 1989) and with adverse changes in both atherogenic and thrombogenic factors (Wilhelmsen et al. 1984; Meade et al. 1986). The effect of weight reduction on cardiovascular disease risk may be mediated through an improvement in associated metabolic changes and blood pressure.

3.2.3 DIABETES, HYPERTENSION AND NEPHROPATHY:

Insusceptible patients, diabetic nephropathy evolves over years and progressed through various phases. The hallmark of diabetic renal disease is the microalbuminuria which is defined as the excretion of albumin at the rate above the normal range, but below the level of albusitx detection, and represents an excretion rate of 20 to 200 mcg/min. Incipient nephropathy is regarded as microalbuminuria being present if two out of three urine samples examined within a six month period. This phase is
uncommon before five years duration of diabetes. Having entered this phase, end stage renal disease usually occurs within further seven years, although the rate of progression varies among patients. Other functional and structural changes arise in association with this phase. A recent report proposed a scheme giving diabetic nephropathy into five stages.

**Stage 1**: Glomerular hyperfunction and hypertrophy. These changes are present at diagnosis. There is a raised glomerular filtration rate (GFR).

**Stage 2**: Normal albumin excretion rate and normal, or only slightly increased blood pressure. Hyperfiltration in the kidney may be present. Structural abnormalities (basement membrane thickening) are present at this stage.

**Stage 3**: Incipient nephropathy. There is a persistent and increasing degree of microalbuminuria. Blood pressure is often elevated compared with normal subjects (Krowelski et al. 1985).

**Stage 4**: Overt diabetic nephropathy. There is a persistent proteinuria with hypertension and fall in GFR.

**Stage 5**: End stage renal failure with uraemia. This stage requires treatment by dialysis or transplantation.

### 3.2.3.1 Diabetes and Microalbuminuria.

Diabetic nephropathy will ultimately develop in 41% of patients with IDDM of up to 40 years duration (Andersen et al. 1983). It has been shown that in comparison to those with normal albumin excretion, persistent proteinuria is associated with a relative 25-fold excess risk of cardiovascular mortality in young diabetic men (Borch-Johnsen et al. 1985). The relative risk is even greater in women, magnified 40-fold (Borch-Johnsen et al. 1985). In NIDDM, the incidence of nephropathy is much less certain, but may be as high as 50% (Fabre et al. 1982). Proteinuria
in NIDDM is also associated with grave cardiovascular prognosis, and the excess risk is independent of associated hypertension, although the presence of both complications exert an additive effects (Nelson et al. 1988). Nephropathy progresses with increasing levels of arterial pressure (Parving et al. 1983). The risk of nephropathy increases three-fold in diabetics when there is a family history of hypertension (Krowlewski et al. 1988).

Persistent microalbuminuria may be responsible for the onset of nephropathy in about one quarter of subjects with NIDDM and a greater number with IDDM (Consensus Statement Proceedings 1989; Christensen & Mogensen 1985). Microalbuminuria in combination with marginally elevated blood pressure, and a decreased creatinine clearance are major predictors of diabetic nephropathy and early mortality (Consensus Statement Proceedings 1989; Christensen & Mogensen 1985). While persistent microalbuminuria may last 15 years or more before overt nephropathy develops (Consensus Statement Proceedings 1989), factors other than strict glycemic control may also determine outcome (Krowlewski et al. 1988). These include the level of blood pressure (Consensus Statement Proceedings 1989; Christensen & Mogensen 1985) genetic tendency of hypertension (Krowlewski et al. 1988), dietary protein intake (Viberti 1989) and racial susceptibility (Cowie et al. 1989). Once persistent proteinuria develops, blood pressure rather than the adequacy of the glycemic control is the major determinant of the time interval before onset of both renal failure and proliferative retinopathy (Hasslacher et al. 1985). In this situation diastolic BP is unusually sustained at a level above 90 mmHg.

A proportion of diabetic patients may have essential hypertension in association with nephropathy. In a study of non-diabetics with essential hypertension and diabetics with overt nephropathy, there was a correlation between mean arterial pressure and rate of urinary albumin excretion.
There was a considerable overlapping of the albumin excretion rate in both diabetics with overt nephropathy and non-diabetic hypertensives (Christensen et al. 1987). On this basis, it may be possible to separate patients with essential hypertension from those with diabetic nephropathy. Majority of patients with diabetic nephropathy have hypertension as a consequence of this complication. The etiology of this type of hypertension has not yet been fully elucidated, but is almost certainly multifactorial and dependent upon genetic and hormonal disturbance.

3.2.3.2 Dislipoproteinaemia in Diabetic Nephropathy:

The effect of early nephropathy on lipoprotein metabolism in IDDM has been studied by various workers (Winocour et al. 1987; Jensen et al. 1988; Walts et al. 1989; Eckel et al. 1981; Vannini et al. 1984; Dullaart et al. 1989; Jones et al. 1989). Some of them have suggested that alterations may be apparent at the stage of persistent microalbuminuria (Jensen et al. 1988; Walts et al. 1989; Vannini et al. 1984; Dullaart et al. 1989; Jones et al. 1989). The dominant abnormality, whilst filtration function is maintained is the reduced circulating HDL and HDL₂ cholesterol concentration. The situation with regards to VLDL and LDL is much less clear. Winocour et al. (1991) reported that cholesterol saturation of the atherogenic intermediate density lipoprotein (IDL₁) fraction is increased in early diabetic nephropathy, but VLDL and "true" LDL composition remains unaltered. Lipoprotein metabolism is further disturbed with advancing renal dysfunction. Nephropathy syndrome leads to an increase in total and LDL cholesterol, and this is compounded by hypertriglyceridaemia and increased VLDL with development of uraemia (Cramp et al. 1975). The effect of renal failure on dyslipoproteinaemia in NIDDM is similar to IDDM. Niskanen et al. (1990) reported that there is reduction in HDL₁ and HDL₂ cholesterol and an increase in serum triglycerides 5 years after the development of microalbuminuria in NIDDM.
3.2.3.3 Vascular Risk Factors in Diabetic Nephropathy:

Hypertension itself is intimately linked with the development of diabetic nephropathy (Sprafka et al. 1988; Anderson et al. 1983), and is often present in proteinuric subjects (Winocour et al. 1987).

Proteinuria is associated with increased transcapillary escape rates of albumin (Feldt-Rasmussen 1986), and it has been suggested that increased glomerular porosity may reflect a state of generalised vascular permeability and endothelial damage (Jensen et al. 1989). This might facilitate the passage of lipoproteins and other atherogenic molecules into the arterial wall, and thus the progression of atherosclerosis.

3.2.3.4 Genetic Influences:

Several reports suggest that there is a genetically determined tendency to hypertension which may be important in the development of diabetic nephropathy. First, hypertension is more common in the siblings of hypertensive patients with IDDM or NIDDM than in the siblings of those who are normotensive (Kelleher et al. 1988). Second, the parents of patients with Type I diabetes who have proteinuria tend to have higher pressure than the parents of patients who do not develop proteinuria (Viberti et al. 1987).

3.2.3.5 Volume Expansion:

Hypertensive diabetic patients have increased plasma volume. The increase in plasma volume is mediated by increased levels of exchangeable body sodium which may precede the onset of hypertension (DeChatel et al. 1977). In diabetic nephropathy there is further increase in the exchangeable sodium as compared to those who do not have nephropathy. The reason(s) for the high levels of exchangeable sodium is not known, although insulin has been shown to promote renal tubular reabsorption of sodium (DeFronzo et al. 1981). The increase in body sodium leads to fluid retention and hence the expanded plasma volume,
favouring development of hypertension.

3.2.4 DIABETIC CARDIOMYOPATHY:

Reviewers of cardiomyopathy in the 1960s observed that populations of patients with primary myocardial disease contained an excess of diabetics (Hamby 1970; Varnaumas et al. 1967). In 1974 a series of diabetic patients was reported with normal coronary arteries by angiography but having clinical or hemodynamic evidence of cardiovascular dysfunction (Hamby et al. 1974). This association have since been extended to diabetics with hypertension (Factor et al. 1980) and chronic renal disease (D. Elia et al. 1979; Rubler et al. 1972). Hemodynamic studies demonstrated a spectrum of abnormalities from simple elevation of the left ventricular and diastolic pressure to severely depressed ejection fraction (D. Elia et al. 1979; Regan et al. 1978). In patients, examined post-partem, multiple histological abnormalities were observed including the deposition of periodic acid schiff (PAS) positive material in the interstitium and small vessels, microvascular endothelium proliferation, interstitial, and perivascular fibrosis and patchy myocytolysis (Factor et al. 1980; Hamby et al. 1974).

Regan et al. (1977) reported the post-mortem examination of 13 diabetics. Nine had no significant coronary disease, although six had been in clinical heart failure at the time of death. Mild thickening of intramyocardial vessels was noted; however the existence of narrowing was equivocal. Marked accumulation of PAS-positive material was seen in the myocardial interstitium, a finding rarely present in the normal individual. Variable degree of patchy fibrosis without inflammatory cells were present. Electron microscopy revealed the accumulation of collagen and amorphous material, presumably the PAS positive material observed, as well as lipid bodies. Muscle samples showed increased triglyceride levels in comparison to non-diabetic normal control.
The same group reported that dogs made diabetic by alloxan developed hemodynamic changes 1 year later which could not attributed to a direct effect of alloxan on the myocardium (Regan et al. 1974). A decrease was seen in left ventricular distensibility characterised by increased left ventricular end diastolic pressure and abnormal responses to saline infusion and pressor agents. Histology showed PAS positive material noted earlier in humans, and accumulation of triglycerides was also suggested.

The same methods were applied to the study of 12 insulin resistant diabetics without significant coronary occlusions by angiography. Eight patients had no prior heart failure by history but they showed abnormal left ventricular pressure volume curves. However, the ejection fractions were within normal limits. The results of responses to angiotensin were same that in experimental animals: the left ventricular end diastolic pressure rose abnormally, but stroke volume failed to increase. These data were felt compatible with an early cardiomyopathy.

The etiology of functional myocardial abnormality is uncertain. Cardiomyopathy often co-exists with microangiopathy (Rubler et al. 1972; Hamby et al. 1974). Other microcirculatory abnormalities in diabetics may co-exist, including platelet defects (both increased aggregation and adhesion) (Colwell 1980), increased plasma viscosity (McMillan 1976), decreased red cell deformability (McMillan 1976), reduced oxygen carrying capacity (Ditzel 1976) and primary capillary basement membrane thickening (Williamson 1977). However, these findings may reflect the increased incidence of independent complications in patients with diabetes of longer duration.

The significance of small vessel disease is also disputed and whether such changes might contribute to myocardial ischemia, remains uncertain (Blumenthal 1960; Pearce et al. 1973; Zoneraich & Silverman 1978). Small vessel disease was noted in 72% of diabetic hearts and 28%
of non-diabetic hearts (Zoneraich & Silverman 1978). However, atrial pacing failed to demonstrate ischemia in one study of diabetes with cardiomyopathy (Regan et al. 1977).

3.2.4.1 Biochemical Changes:
The presence of PAS positive material in histologic specimens of diabetics with cardiomyopathy raises the possibility that glycoprotein deposits may accumulate in myocardial cells and lead to functional abnormalities. In addition to glycoproteins, alterations may also include deposition of collagen and fibrosis (Factor et al. 1980), and lipid accumulation in the form of triglycerides (Bunn et al. 1978). Since the interstitial tissue is the primary site for determining compliance, such deposition could lead to increased stiffness of the muscle.

3.2.4.2 Lipid Metabolism:
Based on a study in spontaneously hypertensive streptozotocin diabetic rats, Rodrigues et al. (1986) reported that the combination of hypertension and diabetes mellitus produces greater myocardial dysfunction. In dose association with the depression of heart function, various biochemical changes including hypoinsulinaemia, hyperglycaemia, hyperlipidaemia and elevated myocardial lipid levels occur in diabetes mellitus. Of those biochemical changes, hyperlipidaemia appears to be a major factor contributing to the development of heart dysfunction.

The most commonly elevated plasma level is that of triglycerides (Denton & Randle 1967) but plasma cholesterol may also be increased. Elevation in myocardial levels of triglyceride and free fatty acids and a decrease in lipoprotein lipase have been reported in diabetes (Harvel et al. 1974). Because of this, in diabetic hearts there is a shift to predominant fatty acid oxidation and lipids may account for 90% of the energy production. Since the oxidation of free fatty acids occurs in mitochondria, they have to be transported from the cytoplasm through the
mitochondrial matrix via a carnitine dependent system. However, it has been reported that alloxan or STZ diabetic rats have reduced myocardial carnitine level (Vauy & Neely 1982). These metabolic abnormalities may relate to the defects in cardiac performance because high lipid levels in plasma or elevated lipid intermediates in the heart are thought to be potentially noxious to the myocardium. They interfere, with various cellular functions by specifically inhibiting enzymes or non-specifically altering the structure of the membrane by detergent like effects. Long chain acyl carnitines (LCAC) have dramatic effect on smooth muscle and heart. Palmitoyl carnitine can increase myocardial calcium current. It has also been shown to exert other effects including inhibition of Na\(^+\)-K\(^+\)-ATPase and Ca\(^{2+}\) ATPase in myocardial sarcoplasmic reticulum. LCAC levels are known to increase in diabetes and may be responsible for the deleterious calcium overload that may occur (Dhalla et al. 1985).

3.2.4.3 Changes in Cardiac Enzyme Systems:

Thyroid hormones have a profound effect on the cardiovascular system. Various studies have demonstrated the presence of hypothyroidism in diabetic patients and animals. This hypothyroidism of diabetes is thought to induce a shift of myosin ATPase isoenzymes. In non-diabetic rats, myosin ATPase is predominantly in the most active V\(_1\) form (72% of the total) and about 13% in the V\(_3\) form. The V\(_3\) form is the slowest of myosin isoenzymes in terms of ATP hydrolysis as well as cross bridge formation and is seen in high concentration in diabetic rat hearts (Dillman et al. 1980). Additional evidence suggesting the role of hypothyroidism in diabetes induced depression of myosin ATPase is provided by studies in which depression of the enzyme in diabetic rats could be prevented by thyroid replacement therapy (Dillman et al. 1982).

3.2.5 LEFT VENTRICULAR HYPERTROPHY AND HYPERTENSION:

Bright (1836) reported on an association among
"Hardness of the pulse", aortic wall thickening and cardiac hypertrophy. Chanutin and Barksdale (1933) were the first to actually demonstrate that experimental induction of systemic hypertension, in a "renoprival model" could produce hypertrophy of the left ventricular myocardial fibres. The increase in heart weight and fibre diameters were directly related to the arterial pressure. However, it was not until Folkow's work in 1956 that the functional consequences of these structural cardiovascular changes in hypertension were seriously considered.

Whatever may be the initiating mechanism for the development of hypertension, the common denominator for all kinds of hypertension in structural changes in the heart and vessels (Folkow 1978, 1982). Furthermore, the development of left ventricular hypertrophy (LVH) constitutes a considerable risk for the morbidity and mortality in hypertension (Carr et al. 1985; Frohlich 1987; Kannel et al. 1969, 1970; Messerli et al. 1983). In the Framingham study LVH in patients with hypertension was associated with higher incidences of stroke, heart failure, and CHD independent of blood pressure level (Kannel 1969, 1970).

Adaptation of cardiac anatomy in hypertensive patients may occur as concentric hypertrophy, eccentric hypertrophy, predominant septal hypertrophy, or any combination of these (Drayer et al. 1983). The pathogenic mechanisms underlying different forms of LVH are not yet clear. Devereux et al. (1983, 1987) have shown that the classic form of concentric LVH (i.e. increased relative wall thickness) and increased peripheral resistance are interrelated in hypertension, whereas, conditions with volume overload such as pregnancy, anaemia, renal failure, obesity etc., result in eccentric LVH (i.e. Chamber dilatation and unchanged radius to wall thickness ratio) (Messerli 1983). Savage et al. (1979) found predominant septal LVH (i.e. Ventricular septal-to-left ventricular free-wall thickness ratio > 1.3) in 4% of their hypertensive subjects. It is not known whether this
abnormality represents a genetically transmitted, abortive variant of hypertrophic cardiomyopathy or an atypical form of left ventricular wall thickening secondary to arterial hypertension.

Data from the Framingham study show that the prevalence of LVH was more common in men than in women and rose with age (Kannel et al. 1969). Age and duration of hypertension have been reported to increase left ventricular mass for a given level of arterial pressure (Devereux et al. 1983), and it has been suggested that the effects of both age and body surface area should be taken into account whenever the effects of hypertension on echocardiographic measurements are assessed. Using this approach, it was found that more than 60% of subjects with mild to moderate hypertension had abnormalities such as septal and posterior wall thickening and increased ventricular mass (Savage et al. 1979).

Sequelae of Left Ventricular Hypertrophy:

At a first glance, an increase in cardiac muscle mass can be considered to be an adaptive mechanism compensating for an increased hemodynamic burden that occurs due to sustained arterial hypertension (Schmieder & Messerli 1990). Initially, this increase in cardiac muscle mass has few functional consequences apart from reducing ventricular wall stress to normal values. However, as hypertensive cardiovascular disease progresses and LVH becomes more severe, the following 4 cardiac disorders or sequelae can be documented.

a) Thickening of the ventricular wall leads to a fall in left ventricular compliance (Smith et al. 1987). This fall in compliance is a passive late diastolic phenomenon and is preceded by a decrease in early diastolic relaxation of the left chamber, which is an active energy requiring process (Lorell & Grossman 1987; Shapiro & Gibson 1988). Thus, the decrease in left ventricular filling seen in patients with LVH results from both diminished early diastolic relaxation and decreased late diastolic compliance.
b) A variety of studies have shown that coronary reserve becomes impaired with the progression of LVH (Polese et al. 1991; Wangler et al. 1982). This decrease in coronary reserve is due to 1) an increased hemodynamic burden (Harrison et al. 1988), 2) an increased left ventricular muscle mass (Strauer 1979), both of which increase oxygen requirements, 3) coronary artery disease, which is a common consequence of long-standing hypertension (Kannel et al. 1970), and 4) microvascular disease, which is a commonly found in patients with essential hypertension even in the absence of LVH (Tomanek et al. 1986).

c) LVH commonly leads to ventricular ectopy. It was demonstrated that patients with LVH have a higher prevalence of ventricular ectopy and more serious arrhythmias than patients without LVH or normotensive subjects (Messerli et al. 1984). Variety of independent studies further confirmed the arrhythmogenicity of LVH (Aronow et al. 1987; Ghali et al. 1991; Levy et al. 1987; McLenachan et al. 1987; Siegel et al. 1990). Ventricular ectopy could well explain the increased prevalence of sudden death observed in patients with LVH.

d) Long-standing LVH leads to impairment of contractive function (Malik et al. 1974). The left chamber becomes progressively dilated and its function shifts to the right on the Frank-Sterling curve (Schlant & Sonnenblick 1990). A decrease in left ventricular pump function heralds the final stage of hypertensive heart disease, i.e. congestive cardiac failure (Kannel et al. 1972; Messerli 1990).

Although arterial pressure has been shown to be a major determinant of LVH, few people with hypertension ultimately develop LVH (Devereux et al. 1987). The weak correlation between arterial pressure and left ventricular mass suggests that other hypertrophogenic factors may be important. These factors include sex, age, race, humoral factors such as the activity of the sympathetic nervous system and the renin-
angiotensin system, whole blood viscosity, intravascular volume (obesity) and perhaps the aetiology of hypertension (Dreifus 1984; Frohlich 1983; Messerli 1983).

Data from Framingham study indicate that, according to electrocardiographic evidence, LVH is not a benign compensatory process but an independent risk factor for congestive heart failure, coronary artery disease, and sudden death (Gorden & Kannel 1971; Kannel et al. 1969). Subsequent investigations revealed that even in its early stages LVH also increases the risk for cardiovascular morbid events (Casale et al. 1986; Kannel et al. 1986).

In the absence of hypertension and atherosclerosis, diabetic patients demonstrate left ventricular dysfunction with lower cardiac output, lower stroke volumes, a prolonged pre-ejection period and shortened left ventricular ejection time (Zarich & Nesto 1989). Metabolic alterations and microvascular diseases are likely to contribute to these changes. In a study of young juvenile diabetics, small vessel disease was present in 72% of normotensive diabetics, but present in 12% of nondiabetic subjects (Hamby et al. 1974). Diabetic animals also demonstrate reduced rate of cardiac contractility and relaxation in the absence of atherosclerosis or frank abnormalities of the microcirculation (Schaffer et al. 1989). Similar to hypertension this is associated with the expression of contractile protein genes that encode for isoforms-characteristic of fetal development. This includes a switch in gene expression from the myosin heavy chain alpha-isoform to β-isoform (Malhotra et al. 1981), and also there is a switch from the V_1 to V_3 form of myosin (Dillman 1980). These cardiac functional abnormalities and isozyme switches are generally reversed by normalisation of glucose levels with insulin or with oral hypoglycemic agents.

LVH does not usually occur in diabetes unless hypertension is present. However, in the presence of
diabetes, damage to the myocardium from hypertension appears to be accelerated.

3.2.6 DIABETES, HYPERTENSION AND RETINOPATHY:

Cohort studies from Wisconsin (Klein et al. 1984) and the Joslin Diabetes Centre (Krolewski et al. 1986) suggest that every diabetic patient will have some retinopathy after 15 to 20 years of diabetes, and between 60% and 65% will eventually progress to proliferative retinopathy. There is little evidence of proliferative retinopathy during the first ten years of diabetes. The rate of development dramatically increases between 10 and 20 years of diabetes (Krolewski et al. 1986; Klein et al. 1989).

Diabetic retinopathy can be divided into different stages (Table: 3.2.2).

Table: 3.2.2
Stages of Diabetic Retinopathy

<table>
<thead>
<tr>
<th>Nonproliferative</th>
<th>Background: Microaneurysms only, or with occasional blotch hemorrhage or flecks or hard exudates.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transitional</td>
<td>Significant blotch hemorrhages or intraretinal microvascular abnormalities or soft exudates or venous abnormalities.</td>
</tr>
<tr>
<td>Preproliferative</td>
<td>Three or more of the transitional lesions present in multiple fields or large amounts of any one lesions in the presence of others.</td>
</tr>
<tr>
<td>Proliferative</td>
<td>New blood vessels on the optic disk; New blood vessels elsewhere; Fibrous proliferation; Preretinal hemorrhage; Vitreous hemorrhage.</td>
</tr>
</tbody>
</table>

Fig.3.2.3 Puts the clinical stages of diabetic retinopathy into perspective and includes diabetic and non-diabetic events.

Diabetes-related events include hyperglycemia, hyperinsulinaemia, altered hemodynamics, abnormal platelet aggregation, genetic factors and growth factors are responsible for producing diabetic retinopathy.
It has been demonstrated that hyperglycemia may damage pericytes (Grunwald et al. 1987). Hyperglycemia may lead to changes in retinal blood flow (Krupin et al. 1979), increased permeability of retinal blood vessels (Prager et al. 1990), and a retinal neuropathy, as measured by early electroretinogram abnormalities (Wu et al. 1990). Recent data on possible activation of membrane-bound protein kinase...
C (Lee et al. 1989) open a new area of potential intervention with regard to diabetic retinopathy. The possible implications of this have not been fully appreciated.

A little-addressed question concerns whether diabetic retinopathy is a vascular or a neural disorder. Although it is frequently considered a vasculopathy, the vessels make up only a small portion of the retina. The retina is principally made up of neural tissue. Some evidence of abnormal electrical transmission has been found in patients before they develop diabetic retinopathy (Finegold et al. 1983).

Hemodynamic changes mediate the evolution from vessel abnormality to retinal abnormality and possibly to the development of retinal ischemia. Hyperglycemia may lead to hyperperfusion of the retina and loss of autoregulation. The entire sympathoadrenal system may be abnormal and contribute to progression of diabetic retinopathy (The Diabetes Control and Complications Trial Research Group 1986).

Leaking vessels and hyperperfusion may lead to increased extravasation of blood and circulating proteins. The defect may be at the point where the retina deals with these abnormal substances or where Human Leukocyte Antigen (HLA) or other immunogenetic factors determine the response of retina to them.

Cardiovascular autonomic neuropathy is associated with a 30-fold increase in the likelihood of proliferative retinopathy (Krolewski et al. 1992). Patients with certain HLA-DR phenotypes have about fourfold increased risk of proliferative retinopathy, whereas patients with low blood pressure appear to be protected from progression of proliferative retinopathy (Janka et al. 1989).

Among diabetic subjects not taking insulin or antihypertensive drugs, the six years incidence of retinal exudates was more than doubled in those with mean systolic
blood pressure of more than 145 mmHg compared with those whose pressure was less than 125 mmHg (Knowler et al. 1980). This association was not substantially confounded by duration of diabetes, age, sex or severity of diabetes as judged by plasma glucose concentration, proteinuria, or neuropathy as measured by impaired vibration sensation or deep tendon reflexes. Thus, it is possible that elevated systolic blood pressure causes some retinal exudates in diabetes (Knowler et al. 1980).
3.3 CHOICE OF ANTIHYPERTENSIVES IN DIABETES-MELLITUS

3.3.1 DIURETICS:

Diuretics have been the keystone of antihypertensive therapy since their introduction 30 years ago. Diuretic-based antihypertensive therapy has been the therapeutic approach used in most of the long-term clinical trials of blood pressure reduction. Majority of these trials with diuretics failed to demonstrate consistent reduction in blood pressure and significant reduction in the incidence of coronary artery disease. However, beneficial reduction in stroke in some studies and congestive heart failure have been observed (MacMahon et al. 1986).

Efficacy, simplicity and low cost are all factors which favour therapy with a low dose of thiazide diuretic. Further, diuretics ameliorate the pathophysiological features thought to be most relevant in hypertension accompanied by diabetes mellitus, namely abnormal sodium retention and exaggerated cardiovascular pressure reactivity (DeChatel et al. 1977; Weidmann et al. 1979). Thiazide diuretics are widely used and generally are effective in early hypertension in diabetic patients. However, thiazide diuretic therapy has several potential side effects (Joint National Committee 1984; Christlieb 1982). Thiazide diuretics in higher doses, may impair glucose homeostasis both in patients with type II diabetes mellitus and in non-diabetic and glucose-intolerant individuals (Amery et al. 1978; Murphy et al. 1982; Vardan et al. 1987; Wilson et al. 1986). They may thus hamper the beneficial effect of improved hypertension on coronary heart disease and other vascular complications (Ames 1983). This effect usually accompanies potassium depletion (Grunfield & Chappell 1983; Heldermann et al. 1983). Thiazides induced hypokalemia may cause a decrease in insulin secretion, increased insulin resistance and impaired control of NIDDM. Administration of
potassium-sparing diuretics or supplementation of potassium may be only a partial solution to this problem. However, potassium sparing diuretics are reported to produce a decline in renal function or hyporeninaemic hyperaldosteronism. Further, potassium sparing diuretics possess a diabetogenic effect (Amery et al. 1978). Many diabetic patients have severe coronary artery disease or cardiomyopathy. In such patients thiazide diuretics may produce ventricular arrhythmias because of decreased serum potassium levels. The cardiovascular benefits of normalised blood pressure are probably also lessened by another metabolic drawbacks. Diuretics can cause elevation of the potentially atherogenic VLDL and LDL-cholesterol fractions, without changing the potentially anti-atherogenic HDL-cholesterol concentrations. However, this effect may be attenuated after several months of therapy (Ames 1983; Weidmann et al. 1985). The role of diuretic-induced rise in serum uric acid in the context of cardiovascular risk factors is much less clear; in rare case it may lead to gout. Diuretics may provoke, usually in elderly diabetic patients with impaired thirst sensation, a hyperosmolar non-ketotic syndrome with coma and death (Fonseca & Phear 1982; Rowe & Mather 1985). In addition, two complications of diabetes mellitus, namely erectile impotence (Lipson 1984) and orthostatic hypotension, may be aggravated with diuretics. Thiazide diuretics can reduce glomerular filtration rate (GFR) and renal blood flow (RBF) (Rudd & Blaschke 1985). The antihypertensive efficacy is sharply diminished in individuals with renal insufficiency (Lowenthal & Dickerman 1983).

If diuretics still remain among the first choice monotherapies in hypertensive patients with diabetes mellitus, which is controversial at present, low doses should be prescribed (not more than 25 mg/day of chlorthalidone or hydrochlorothiazide). Bearing in mind financial considerations, if necessary to remember that continuous monitoring and control not only of glucose
homeostasis, but also of potassium and lipids as well as kidney function, are mandatory. Thus, diuretics should be started as the initial drugs only under special circumstances, for example if oedema is a problem or if heart failure is present and ACE inhibitors contraindicated. Nevertheless, low-dose diuretics are often a reasonable complement in cases where the therapeutic aim is not reached by monotherapy with another drugs.

3.3.2 \( \beta \)-ADRENOCEPTOR ANTAGONISTS:

Cardioprotection and antianginal effects, the main advantage of \( \beta \)-blockers, are welcome in hypertensive diabetic patients because most of the mortality associated with these conditions is associated with cardiovascular complications. Many \( \beta \)-blockers normalise blood pressure when administered on a once daily schedule, and they all reduce tachycardia, which is the first sign of autonomic neuropathy. However, \( \beta \)-adrenergic antagonists produce a profound influence on catecholamine mediated metabolic effects. Since insulin secretion is stimulated through \( \beta_2 \) receptors, non-selective blockade of both \( \beta_1 \)- and \( \beta_2 \)-receptors could theoretically lead to impaired glucose homeostasis by a decreased insulin output in patients with type II diabetes (Christlieb & Maki 1980). It has been found that non-selective \( \beta \)-blocker hypoglycemic episodes by blocking glycogenolysis in muscles and lipolysis in adipose tissue, thereby reducing the substrates for both gluconeogenesis and ketogenesis (Christlieb & Maki 1980; Deacon et al. 1977; Lager et al. 1979). They also diminish patients awareness of hypoglycemia (Barnet et al. 1980). Further, non-selective \( \beta \)-blockers can provoke hypertensive crisis during hypoglycemia, as over stimulated alpha-receptors dominated arteriolar constriction is no longer counterbalanced by \( \beta_2 \)-mediated vasodilatation (Ryan et al. 1985). These effects can probably be avoided by choosing \( \beta_1 \) selective blockers. Recently, there has been increasing interest in a possible association between reduced insulin
sensitivity and development of hypertension (Ferrannini et al. 1987; Reaven 1988). In a study, six months treatment with atenolol was found to decrease insulin sensitivity by 21%. This was accompanied by significant increase in fasting plasma insulin, blood glucose and glycosylated hemoglobin (Pollare et al. 1989). In an another study, four months treatment either with metoprolol (200 mg/day) or atenolol (50 mg/day) significantly decreased the insulin mediated glucose uptake as measured with euglycemic hyperinsulinaemic clamp technique (Pollare et al. 1986). This was accompanied by significant increase in fasting plasma insulin, blood glucose and glycosylated hemoglobin values.

Another area of concern with β-blocker is their effect on plasma lipid. Several investigators have assessed the effects of atenolol on plasma lipids in patients with hypertension in the light of the association between increased plasma triglycerides and mortality in patients with cardiovascular disease. Most of these studies involved between 20 to 100 patients with hypertension and compared the effect of atenolol with those of other β-adrenoceptor antagonists. Once daily administration of atenolol 50 or 100 mg for 1 to 3 months significantly increased the plasma concentration of triglycerides by 20 to 34% (Day et al. 1982; Leren et al. 1982; Lithell et al. 1986) and VLDL and triglyceride levels by 28 to 46% (Day et al. 1982; Lithell et al. 1986). HDL-cholesterol levels were either decreased by 7% (Day et al. 1982) or unchanged (Leren et al. 1982). Total cholesterol plasma concentrations were increased by 3 to 5% (Day et al. 1982; Leren et al. 1982). Similar changes were observed in patients with hypertension treated with atenolol 50 mg to 100 mg daily during studies of 5 months to 3 years' duration (Fogari et al. 1989; 1991; Frick et al. 1987; Karlson et al. 1988). Changes in triglycerides and total cholesterol levels were accompanied by an increase in VLDL cholesterol, VLDL triglycerides and apoprotein B levels and a decrease in levels of apoprotein AI and AII (Chanu et al. 1991; Lithell et al. 1986; Vyssoulis et al. 1991).
Similar changes in lipid metabolism have been observed in non-insulin dependent diabetic patients with hypertension (Feher et al. 1990).

The increase in plasma concentrations of triglycerides associated with atenolol were less pronounced than those occurring with propranolol (24 vs 51%) after 3 months (Day et al. 1982) and 6 months (20 vs 38%) (Fogari et al. 1990). The changes in plasma lipid concentrations observed within 6 months of starting atenolol treatment (50 to 200 mg/day) tend to decrease after 2 years of continued administration (Fogari et al. 1990; Middeke et al. 1987). A 3-week placebo-controlled study in patients with hypertension and noninsulin-dependent diabetes previously treated with atenolol for at least a year, suggests that atenolol-induced changes in lipoprotein profiles are reversible following treatment withdrawal (Feher et al. 1988). It has been reported that chronic treatment with atenolol in streptozotocin induced diabetic rats could not prevent diabetes induced hyperlipidaemia, cardiomyopathy and cardiac dysfunction. The cardiac dysfunction and cardiomyopathy were rather found to be aggravated (Bangaru et al. 1991).

Renal functions seem to be altered by non-selective β-blockers. Prolonged use of propranolol produced a 10 to 20% reduction in GFR and RBF (Epstein & Oster 1982). Results from studies investigating the effects of atenolol on renal function have been inconclusive. Some investigators reported atenolol treatment to cause a marked decrease in GFR (Cook et al. 1986), creatinine clearance or renal vascular resistance (Furman et al. 1986), while others failed to show any significant effect on these parameters (Brater et al. 1983; Dreslinski et al. 1982). Atenolol does not appear to have any statistically significant effect on RBF (Dreslinski et al. 1982) or urinary prostaglandin E₂ and F₂alpha excretion (Rathaus et al. 1983) in patients with hypertension. However, reduced albumin excretion rates (~36%) were observed in patients with hypertension, non-
insulin dependent diabetes and persistent albuminuria (Stornello et al. 1991). In addition, significant decrease in serum $\beta_2$-microglobulin levels following administration of atenolol 50 mg daily for 8 weeks to non-insulin dependent diabetic patients with normal renal function indicates a possible improvement in GFR in these patients (Koh et al. 1985).

Finally there are well known problems of physical exercise, cold peripheries and Ranaud's phenomenon with $\beta$-blockade. Thus, the use of $\beta$-blockers in diabetes-mellitus does not seem to be justified.

3.3.3 CALCIUM CHANNEL BLOCKERS:

Calcium antagonists are being used increasingly in the treatment of hypertension. Long term studies demonstrated that calcium channel blockers significantly reduced blood pressure without aggravating renal, cardiovascular, cerebrovascular or peripheral vascular disease, diabetes-mellitus or asthma (Bondi & Ciofalo 1988; Croog et al. 1986; Frishman et al. 1989; Holzgreve et al. 1991; MacGregor et al. 1990; Bursztyn et al. 1985). In vitro experiments have shown that insulin secretion is dependent upon calcium influx into pancreatic $\beta$-cells. Calcium antagonists nifedipine, diltiazem and verapamil have consistently been shown to inhibit insulin release in vitro and thereby may affect glucose tolerance in animal models and also in humans (Chellingsworth et al. 1989; Gill et al. 1987; Parent et al. 1989; Davis et al. 1975). Insulin levels tend to decrease (Charles et al. 1981; Ferlito et al. 1981; Shah et al. 1995) whereas glucagon release tend to increase after nifedipine administration (Parent et al. 1989). Impairment of insulin secretion by nifedipine has been reported in non-diabetic individuals (Guigliano et al. 1980) and in patients with impaired glucose tolerance (Charles et al. 1981). Nifedipine has shown to be diabetogenic when administered for a short period (< 1 month) to subjects with or without cardiovascular disease and with normal or reduced glucose
tolerance (Bhatnagar et al. 1984; Chellingworth et al. 1989; Perlito et al. 1981; Guigliano et al. 1980; Sando et al. 1983). Plasma glucose levels are increased during an oral glucose tolerance test after 12 weeks of nifedipine administration to 8 non-diabetic hypertensive patients (Palumbo et al. 1988). Fasting plasma glucose levels also increased in 19 patients with hypertension and non-insulin dependent diabetes-mellitus when treated with nifedipine for 4 to 6 weeks (Chellingsworth et al. 1989).

In contrast, a large number of single dose studies have shown that nifedipine has no significant effect on glucose tolerance in healthy volunteers and in subject with impaired glucose tolerance or diabetes (Abadie & Passa 1984; Andersen et al. 1982; Brauman et al. 1984; Deedwania et al. 1984). Nifedipine treatment for 6 to 24 weeks does not produce any effect on glucose tolerance in patients with hypertension associated with or without diabetes (Baski et al. 1990; Fujii et al. 1990; Kazumi et al. 1989; Pasanisi et al. 1986) and in diabetic rats (Shah et al. 1995). Despite the ambiguous findings, the balance of currently available data suggest that nifedipine does not have diabetogenic potential. More studies are however, thus required to examine the long term effects of these drugs and specially their overall glycemic control as assessed by serial blood glucose measurements, rather than simply their short term effect on glucose tolerance.

Several experiments in animal models, especially cholesterol-fed rabbits, have indicated that nifedipine may reduce accumulation of atherosclerotic components and therefore slow the progression of atherosclerotic lesions (Gotto 1990). Further, nifedipine has inhibited proliferation of cultured smooth muscle cells from rat aorta (Triggle 1989), and is known to inhibit in vivo platelet aggregation in human (Sorkin et al. 1985). However, conflicting data are available as far as the influence of nifedipine on lipid profile in patients with non-diabetic or
diabetic hypertension is concerned. A number of studies have shown that nifedipine does not produce any significant effect on lipid parameters (Birkebaek et al. 1989; Lehtonen et al. 1986; Pasanisi et al. 1986; Vessby et al. 1983; Ohman et al. 1985). In contrast Houstan et al. (1990) recorded significant increase in HDL, HDL-2 and apolipoprotein A-I and A-II levels after the administration of nifedipine. In a recent study, nifedipine has been shown to prevent diabetes induced hyperlipidaemia, hyperglycemia, cardiac dysfunction and cardiomyopathy in streptozotocin induced diabetic rats (Shah et al. 1995). Afzal et al. (1988) demonstrated that verapamil is capable of preventing diabetes-induced myocardial changes, without affecting the hyperglycemic status. This also supports the involvement of calcium ions in the cardiac pathology during diabetes.

Bauer et al. (1985) reported that short or long-term administration of calcium antagonists did not produce any consistent changes in GFR or effective renal plasma flow. However, in patients with hypertension with or without concomitant glomerulonephritis, increases in GFR and RBF when treated with nifedipine or diltiazem (Reams et al. 1988; Sunderrajan et al. 1986). In contrast, Bellini et al. (1984) showed a single oral dose of nifedipine significantly reduce GFR in hypertensive patients on normal or low sodium diet. Several reports demonstrate an acute natriuretic effect of calcium antagonists without any changes in renal function although the magnitude of the effect appears to be variable with different agents (Bauer et al. 1985; Kubo et al. 1986). However, there has been one report of acute, reversible deterioration in renal function after the use of nifedipine in four patients with chronic renal insufficiency (Diamond et al. 1984).

The long term outcome of NIDDM treated with calcium antagonists remains to be investigated further and there is as yet almost no substantial literature concerning the calcium antagonist therapy in patients with IDDM. It would
be preferred to start with low to moderate dose of calcium antagonists rather than a diuretic or a \( \beta \)-blocker.

3.3.4 VASODILATORS:

They are commonly used as third line drugs in the management of hypertension. It has been reported that hydralazine does not affect glucose tolerance in human studies. Hydralazine is also reported to be beneficial in the prevention of coronary and other atherosclerotic disease seen during diabetes (Roadrigues et al. 1986). Vasodilators have been demonstrated to increase RBF and may have a beneficial effect on renal function (Brazy et al. 1989; Spitalawai et al. 1986). Prazosin, a selective alpha-blocking agent, acts as an indirect vasodilator to reduce blood pressure. Several studies with prazosin have demonstrated a decrease in total cholesterol and triglyceride levels as well as increase in HDL cholesterol levels (Kokuba et al. 1982). Chronic treatment with prazosin in streptozotocin induced diabetic rats did not alter the diabetes induced hyperglycemia and hyperlipidaemia. However, it prevented the diabetes induced cardiac dysfunction and cardiomyopathy (Bangaru et al. 1991). Lowenstein (1985) demonstrated a consistent beneficial effect of prazosin on plasma in hypertensive patients. It has however been reported that the administration of a single dose of prazosin (2 mg) causes an increase of plasma glucose in patients with chemical diabetes (Barbieri et al. 1980). In contrast, chronic therapy (3 mg/day) for 1 week significantly improve glucose tolerance with slight increase in insulin levels in a group of diabetic patients (Dzau et al. 1980). Alpha\(_1\)-blocking agents have also been shown to improve hyperinsulinaemia and abnormal glucose-tolerance curves in obese hypertensive patients (Pollare et al. 1988; Swislocki et al. 1989). Prazosin and terazosin do not produce any significant effect on renal hemodynamics. The alpha\(_1\)-blockers can produce orthostatic hypotension after the first dose, especially in elderly and diabetic...
hypertensive patients who may have abnormal autonomic response.

3.3.5 ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS:

The RAS is known to play a key role in the regulation of blood pressure as well as in sodium-potassium homeostasis (Page & Bumpus 1974). The ACE inhibitors are useful in the treatment of hypertension and congestive heart failure (CHF) primarily through inhibition of RAS system. Studies in both animals and humans have confirmed a reduction in blood pressure following ACE inhibition (Kostis et al. 1987). In normotensive subjects, a single dose of an ACE inhibitors decreases BP by 5-20 mmHg (Kostis et al. 1987). ACE inhibitors lower BP effectively in both types of diabetes when associated with hypertension. Moreover, their profile make them most appropriate in patients with hypertension with limited cardiac reserve or heart failure not uncommon in diabetic patients (Dominguez et al. 1987; Lanza et al. 1985). Most important, in hypertensive diabetics ACE inhibitors seem to be as metabolically neutral. Recent studies (Jauch et al. 1987; Catalano et al. 1992; McMurry & Fraser 1986; Pollare et al. 1989; Rett et al. 1988; Santoro et al. 1992; Torlone et al. 1991) have shown that captopril improves insulin sensitivity in diabetic patients. Several cases of hypoglycemia have been reported in chronic hyperglycemic NIDDM patients receiving oral hypoglycemic agent after initiation of captopril (Arauz-Pacheco et al. 1990; Ferriere et al. 1985; Relt et al. 1988a) or enalapril therapy (Arauz-Pacheco et al. 1990; Ferriere et al. 1992). In sort term studies using euglycemic clamp technique, an increase in insulin-mediated glucose uptake i.e. increased insulin sensitivity after ACE inhibitor treatment in NIDDM patients (Jauch et al. 1987; Torlone et al. 1991). Furthermore, Prince et al. (1988) reported an improvement of insulin sensitivity with a slight reduction in fasting blood sugar during enalapril therapy. Pollare et al. (1989) also observed an improvement in insulin sensitivity associated with captopril. These effects of ACE inhibitors on insulin
sensitivity have mostly appeared in the patient groups that are considered to be insulin-resistant.

In contrast, Baba et al. (1993) observed that 6 months of treatment with enalapril 20 mg/day caused no significant alterations in serum insulin or plasma glucose response to an intravenous glucose tolerance test in hypertensive non-insulin resistant patients. Allemann et al. (1992) also did not find any significant change in insulin sensitivity assessed by intravenous glucose tolerance test after 1-week and 3-week treatment with fosinopril 20 mg/day in healthy normotensive subjects. Many other studies with enalapril, captopril or cilazapril failed to show significant effect on insulin sensitivity on glucose tolerance in individuals who have no obvious insulin resistance (Seghieri et al. 1992; Passa et al. 1987; Chen et al. 1992; Santoro et al. 1992).

Enalapril does not alter plasma or urinary excretion of potassium, creatinine and aldosterone in diabetic hypertensive patients (Zanella et al. 1990). Serum fructosamine, peptide C and glycosylated hemoglobin levels were not significantly modified in diabetic hypertensive patients (Ferrier et al. 1992). Chronic treatment of enalapril in streptozotocin induced diabetic rats significantly decreased total cholesterol, LDL-cholesterol and triglyceride levels and increased HDL-cholesterol levels (Bangaru et al. 1992).

Captopril 25 mg twice daily for 3 months in hypertensive patients significantly reduced total cholesterol levels, LDL-cholesterol levels, the ratio of total cholesterol : HDL-cholesterol and apo C-III levels (Catalana et al. 1992). In an another study, when enalapril 20 mg/day for 10 weeks was given to diabetic hypertensive patients, it did not modify the serum total and lipoprotein lipid fractions, or apolipoprotein AI and B (Ferrier et al. 1992). However, a recent study (Libertti & Catalona 1993) demonstrated that enalapril significantly reduced the total
cholesterol, triglyceride and LDL-cholesterol in essential hypertensive patients.

Chronic enalapril treatment improved cardiac function and also prevented cardiac hypertrophy and cardiomyopathy in diabetic hypertensive rats (Bangaru et al. 1992). It has been demonstrated that ACE inhibitors prevent the development of left ventricular hypertrophy (LVH) in animals and also induced regression of LVH in animals and humans with established hypertension (Hansson & Dahlof 1990). After myocardial infarction, ACE inhibitors also prevent cardiac remodeling, which is associated with cardiac ventricular dilation and dysfunction (Pfeffer et al. 1988).

Captopril in 10 diabetic patients with severe diabetic nephropathy, reduced proteinuria within two to four weeks (Taguma et al. 1985). These results were confirmed by Hommel et al. (1986) in hypertensive diabetic patients with clinical nephropathy. Captopril 50 mg twice daily induced a significant reduction of albumin excretion rate without any significant modification of GFR (Hommel et al. 1986), whereas, in hypertensive diabetes without established nephropathy, this may not be the case (Winocour et al. 1986). These concordant studies in diabetic patients with severe nephropathy demonstrated that ACE inhibitors are effective and may postpone end stage renal failure. ACE inhibitors have a protective effect on kidney that seems to be independent of their antihypertensive effect (Lewis et al. 1993). In a randomised placebo-controlled trial in 409 patients with insulin-dependent diabetes and nephropathy (urinary protein excretion at least 500 mg/24 hrs), most of whom were hypertensive, captopril halved the combined risk of death or requirement for dialysis or renal transplantation during the 3 years' follow up (Viberti et al. 1994). However, there have been some controversy about the use of ACE inhibitors in patients with renal failure. On the ground that reducing blood pressure so effectively might cause a reduction in renal perfusion (Watson et al. 1983).
The diabetic patients with nephropathy may suffer from undesirable side effects like hyperkalemia, initial acute increase in creatinine levels. The dose of ACE inhibitors must be adapted to the level of creatinine clearance (Ferguson & Vlasses 1987). Recently, results of a US study clearly show that the antiproteinuric effect of enalapril does not predict an attenuation in the rate of progression of established clinical diabetic nephropathy (Bauer et al. 1992). Dzau et al. (1981) found that effective RBF and GFR increased significantly with captopril. It has been reported that captopril in hypertensive patients with nephropathy does not produce any significant change in renal function, proteinuria and glycosylated hemoglobin (Valvo et al. 1988). These controversial effects of ACE inhibitors on renal functions require further study. Overall, it seems that ACE inhibitors may be a better option for the treatment of hypertension in diabetic patients.

3.3.6 CENTRALLY ACTING AGENTS:

Centrally acting antihypertensive agents like clonidine, methyldopa and guanabenz are commonly used drugs for the management of hypertension and have been shown to be effective forms of monotherapy (Bosanac et al. 1976; McMahon et al. 1977; Holmes et al. 1983; Weber et al. 1976). These drugs mainly act within the central nervous system and their antihypertensive effect is attributed to a decrease in sympathetic outflow (Baum & Shropshire 1976; Weber et al. 1983; Jaju et al. 1966). In hypertensive patients, guanabenz lowers blood pressure by decreasing peripheral resistance. At the same time, there appear to be only minimal changes in heart rate, myocardial contractility or cardiac output (Shah et al. 1976). Clonidine, when given directly into the cisterns (Kobinger & Walland 1967) or the intracerebral ventricles (Schmitt & Schmitt 1969) decreases both blood pressure and heart rate. Methyldopa in 10 insulin dependent diabetic patients did not produce any significant increase in fasting blood sugar or total cholesterol levels (Benfield & Hunter 1982). Neither plasma glucose concentration nor the
diabetic therapy requirements of the diabetic hypertensive patients were altered by guanabenz treatment. In fact there was a small decrease in total cholesterol concentrations (Weber et al. 1984). Ishii et al. (1985) reported that the usual rise in insulin levels in response to glucose (750 mg/kg i.v.) was attenuated in normotensive rats received 10 days of clonidine treatment which is mainly attributable to the hyper-responsiveness developed in the pancreatic β-cell. However, the serum glucose levels of Wistar Kyoto and Spontaneously hypertensive rats were elevated whereas the concentrations of insulin were decreased on day 10 of a continuous subcutaneous infusion of clonidine (Lewis et al. 1989). In maturity onset diabetes, clonidine has been reported to decrease glucose tolerance without any significant effect on glycemic control (Guthire et al. 1983).

In general, guanabenz and clonidine appear to work well in patients with renal insufficiency and does not usually cause deterioration in renal function (Bauer 1983; Hoobler & Sagastume 1971). Clonidine does not, alter RBF or GFR during long-term therapy (Schmitt & Schmitt 1969). Guanabenz has been shown to increase GFR and sodium excretion in dogs (Stranadhooy et al. 1982). However, it has not been shown, whether clonidine has the same ability as guanabenz to promote increase in sodium and water excretion. Clonidine has a modest inhibitory action on renin-aldosterone axis (Weber et al. 1976).

Despite, the long-term availability of clonidine for commercial use, there is a lamentable paucity of data on its effects on lipid profile.

The sympathetic nervous system is increasingly implicated in the pathogenesis of hypertension. Furthermore, evidence indicates that an excess of catecholamines may facilitate cardiac hypertrophy, arrhythmias, atherosclerosis and hyperperfusion of kidney. Activation of the sympathetic...
nervous system, as indicated by the plasma concentration of norepinephrine is a marker for poor outcome in heart failure (Cohn et al. 1984). The consequences of increased sympathetic activity and elevated levels of catecholamines can be minimised most directly by reduction of sympathetic outflow at its point of origin, within the central nervous system. In this respect, the use of centrally acting drugs seems to be more reasonable than the use of vasodilator compounds that decrease peripheral resistance, partly because centrally acting drugs also modulate reflex response triggered by changes in arterial blood pressure.