CHAPTER I

Introduction and Review Litterature

Diabetes mellitus is a genetic disorder in which superimposed environmental factors bring out the phenotypic expression of the disease (Marvin, D. 1988). It is a disorder of metabolism of carbohydrate, protein, and fat associated with an absolute or relative insufficiency of insulin secretion accompanied by various degrees of insulin resistance (Derek, L. 1996). In its fully developed clinical expression, it is characterized by fasting hyperglycemia or by levels of plasma glucose above defined limits during a glucose tolerance test and, in most patients with long - standing disease, by microangiopathic and atherosclerotic macrovascular disease (Daniel, P. 1997).

Diabetes millitus is subdivided into two major categories , insulin - dependent diabetes mellitus (IDDM) and non - insulin dependent diabetes mellitus (NIDDM) .

Type I : Insulin - dependent Diabetes Mellitus (IDDM)

Type I or insulin - dependent diabetes mellitus (IDDM) occurs in approximatly 10% of all diabetes, (Harold, 1991). IDDM, an autoimmune - mediated destructive disease of β - cell, affects children and young adults with an inherited susceptibility linked to a class II major histocompatibility

complex molecule (Roger, 1991). Usually there is a symptomatic onset to severe insulin insufficiency (polyuria, polydipsia, polyphagia, weight loss, fatique). In addition, the signs of ketosis may occur in this severve disease. Insulin dependency implies that administration of insulin is essential to prevent spontaneous ketosis , coma , and death (Harold, 1991).

Type II : Non - insulin - dependent diabetes mellitus (NIDDM)

The second type of diabetes , type II or non - insulin dependent diabetes mellitus (NIDDM) is the most common form of human diabetes, also has a genetic basic that is commonly expressed by a more frequent familial pattern of occurrence than is seen in IDDM.

In contrast to IDDM, there is no consistent reduction in β - cell number in NIDDM (Roger, 1991) and the patients with NIDDM may have a body weight that ranges from normal to excessive. The intake of excessive calories leading to weight gain and obesity and resulting in insulin resistance are important factors in the pathogenesis of NIDDM. A genetic defect in the insulin secretory response to nutrients may be brought out for the first time when the insulin receptor is partialy response to the insulin .

The various clinical syndromes associated with diabetes and the final pathological features are also shared by all major diabetic complications. **Vascular disease , such as macroangiopathy and**

microangiopathy is one of the most serious chronic complications which are found in this disease.

The microvascular complications or microangiopathy of diabetes include retinopathy, nephropathy and neuropathy. Most investigators now agree that diabetic microvascular complications result from the interaction of multiple metabolic, genetic and other factors, of which chronic hyperglycemia is the most significant (Marvin, 1998).

The clinical and animal model data point out that chronic hyperglycemia appears to be the central initiating factor for all types of diabetes microvascular disease. Duration and magnitude of hyperglycemia are both strongly correlated with the extent and rate of progression of diabetic microvascular disease, although factors such as genetic determinants of tissue response to injury, hypertension , and dyslipidemia clearly influence the clinical cause (Hanoch , et al., 1967 ; James, et al., 1995).

Pathogenesis of diabetic microangiopathy which may includes morphological change and functional change are found in biopsy materisls the thickening of capillary basement membranes . (Williamson, 1977.). Collagen deposition around capillary microvessels is enhanced (Mc Millan, 1966.) and the metabolic changes are also found in microvascular walls (Brownlee, 1988.). Potentially, these mechanisms may weaken the microvascular walls and make them less resistant to the hemodynamic forces acting on them. Formation of aneurysm may

ensure, especially with rarefaction of endothelial cells, which has been observed in microvessel (Kohner, 1970 ., Kohner , 1986.).

Macroangiopathy has come to be identified in the diabetic with a set of structural changes in the vessel wall. Dissociation between structural changes in the arterial wall and the frequency of the clinical manifestations of coronary heart diseases are usually found in diabetic patients. Some of the abnormalites in the repolarization (ST) segment of the electrocardiogram which leads to congestive heart failure are usually lumped into the macrovascular disease. Several studies have also been carried out in induced diabetes rats and summarized the effects of acute and chronic diabetes in animals (Fein, 1985.). Acute diabetes results in a diminishing response of cardiac output to increase filling pressure while superimposed ischemia causes accelerated cardiac failure with prolonged recovery of cardiac performance. Further, acute diabetic rats appear extremely sensitive to alterations in after - load , with diminished systolic response to high levels of after - load.

In 1979, Pogatsa and co - workers observed similar evidence of diminishing left ventricular compliance in chronic diabetic dogs with severe hyperglycemia . In a latter study using this same model, coronary artery occlusion produced significantly larger infarcts in the diabetic cohort compared with control animals, confirming the apparent additive effects of ischemia and diabetes on ventricular function (Palik , I . 1982.).

Myocardial dysfunction usually related to coronary artery disease and systemic hypertension occurs frequently in diabetes. **These evidences indicate that it is a primary diabetic cardiomyopathy.** Vascular disease and its sequelae are the most important cause of morbidity and mortility in humans. The pathophysiology of vascular disease may involve the enhancement of vasoconstriction , increase of platelet vessel wall interaction, adherence of monocytes, migration and proliferation of vascular smooth muscle cells, and increased matrix production (Ross, R. 1993.). Vascular disease has developed and further caused the left ventricular changes. The end results are congestive heart failure and death may accur. Cardiovascular therapy, therefore, has to interfere with basic processes in order to avoid the development of vascular disease and at later stages to prevent its sequelae.

Several studies demonstrated that vascular functions, including vasomotion, proliferation of vascular smooth muscle cells and oxidizing LDL (low density lipoprotein) on endothelial cells mediated by increasing intracellular calcium, are response to local changes such as cells and their environments (Daugherty, A. 1987., Sachinidis, A. 1993., Simons, M. 1995.).

Henry & Bentley (1981) first demonstrated that a calcium entry blocker (nifedepine) inhibited atherogenesis in dietary - induced hypercholesterolaemia in rabbits.

In 1985 Anthony and co - workers studied effects of calcium antagonist (nicardipine) which suppress the formation of atherosclerotic lessions and accumulation of cholesterol in rabbits. They were fed with 2% cholesterol diet for 8 weeks. Calcium antagonist effects on antiatherosclerotic mechanisms through antihypertensive activity or suppression of lipid uptake by scavenger cells. Possibility exists that this calcium antagonist promotes cholesterol ester catabolism and cholesterol clearance by reducing monocyte adhesion to activated endothelium (Andrew, et al., 1992).

However, some other studies indicated that nicardipine in clinical trial has no effect on advanced coronary atherosclerosis but may retard the progression of minimal lesion. (David, W., et al. 1994)

In 1980, Lieberman discovered that elevated levels of serum angiotensin-converting enzyme were associated with in diabetic patients. Another studies indicated that angiotensin-converting enzyme were localized in vascular endothelial cells by fluorescence method (Caldwell, P. 1980).

Later, in 1989 Naftilan demonstrated the effects of angiotensin II leads to the rapid rise in the steady-state m RNA levels of the proto-oncogenes c-fos, c-myc and c-jun. Also, angiotensin II induce platelet-derive growth factor that increases smooth muscle cell protein synthesis. In addition, the reduction of the smooth muscle cell size and medial smooth muscle cell content in the observed (Naftilan, et al. 1992).

The molecular mechanism by which angiotensin II results in an increase in smooth muscle cell growth is not well defined at this point. Reduction of the smooth muscle cell size and medial smooth muscle cell content in the Wistar-Kyoto rats after captopril treatments are observed (Naftilal, et al 1992). However, possibility angiotensin II and any contractile agonist that increase intracellular calcium via activation of protein kinase C results in an increase of new transcription of the early growth response genes.

Increasing of the myocardial infarction is one of diabetic comlications. In 1995, Keidar, demonstrated the stimulatory effects of angiotensin II on macrophage mediated oxidation of LDL and also on cellular lipid peroxidation. This may related to the acceleration of atherosclerosis. In addition, angiotensin II may exert its effect on several other properties of macrophage including foam cell formation and the secretion of cytokines and growth factors.

According to several observations highlighted the coincidence of the diabetic cardiomyopathys and atherosclerosis. Moreover only calcium channel blockers have been tested for their effects on human atherosclerosis. Nifedepine and nicardipine prevented the progression of small atherosclerotic lessions, but large plaques were unchanged (Waters, D. 1990., Lichtlen, P.R. 1990.). Unfortunately the effect of angiotensin converting enzyme inhibitor (ACEI) such as captopril that retarded the

progression of atherosclerosis has been demonstrated only in hyperlipidemia rabbits (Chobanian, 1990.).

Interestingly, angiotensin converting enzyme inhibitors and calcium channel blockers have a complementary profile, both in their hemodynamic and local vascular actions. Hence, combination therapy with these two classes of drugs appears particulary in hypertension patients for reduce blood pressure (Kloke, et al . 1989). However this combined therapeutic effect on diabetic cardiovascular complications has not yet been demonstrated.

Therefore , the major objectives of this investigation are :

1) To study the effects of nicardipine on cardiovascular complications in diabetic rats .

2) To study the effects of nicardipine combined with cilazapril on cardiovascular complications in diabetic rats.