CHAPTER I

INTRODUCTION AND LITERATURE REVIEWS

Definition of diabetes mellitus

Diabetes mellitus is a disease syndrome best characterized as a state of chronic hyperglycemia with the various of aetiologies. It may present with acute symptoms that include thirst, polyuria and weight loss, and can progress to life threatening ketoacidosis or hyperosmolar coma. Subacute symptoms include the above, together with puritis vulvae, balanitis, other skin infections, unusual fatigue or visual impairment. The clinical suspicion of diabetes is strongly enchanced by glycosuria with or without ketonuria, but biochemical confirmation of the diagnosis is required by accurate measurement of blood glucose levels using a specific enzymatic glucose assay (Natirass and Santiago, 1984).

Pathophysiology of diabetes mellitus.

Diabetes occurs when the blood glucose is too high as a result of a deficiency of available, effective insulin. This lack can be absolute when the pancreas does not produce enough insulin (or produces none at all) or relative, when the pancreas produces a "normal" amount of insulin, but for some reason the body needs more than a normal amount of insulin or the insulin is made ineffective and the pancreas cannot produce enough to compensate. As a result of these deficiencies,the cells lack of fuel, and the body suffers from a lack of energy. People with

diabetes complain of weakness and tiredness, and a usually active young child may be tired or listless. When the cells are starved of their fuel, the body recognized that not enough food has been eaten and triggers a sense of extreme hunger, called polyphagia. The glucose level in the blood rises because it is not used. At sametime, out of desperation, the body turns to stored fuels-glycogen, fat and protein to try to meet its energy needs. The level of glucose in the blood continues to rise, as does the blood level of fats. (Natirass and Santiago, 1984) The huge excess of unused glucose circulates through the Kidney, which normally rescues useful glucose from the filtered fluid to keep it from being lost in the urine. There is a level of blood glucose, however known as the renal threshold, above which the kidneys cannot keep up with the job of retrieving glucose, and it escapes into the urine. Once this level (usually 160 to 180 mg%) is passed, glucose spills into the urine as form an overflowing dam. As the blood sugar rises, excess glucose appears in the urine. When diabetes is severe, a large proportion of the body's energy needs are lost into the urine in the form of glucose (Davidson, 1991). The body knows when the urine is too loaded with sugar and is too concentrated and tries to dilute it by allowing more and more fluid to flow through the kidneys. Hence, the person with high blood glucose levels and glycosuria experiences frequent urination of large amounts of fluid, known as polyuria . With the fluid loss, the body senses of dehydration, and the thirst center is triggered, making the individual drink more fluid. This

increased thirst is known as polydipsia This vicious cycle of glucose and water loss, and the attempts to correct this loss, lead to the classic symptoms of diabetes. All of these are due to the body's inability to use glucose properly as the body fuel (Beason, 1989).

The National Diabetes Data Group and WHO divided diabetes into type I and type II, there is accumulating evidence for heterogenity within each of these groups and of overlap between the two major types of diabetes (Palmer and Lernmark, 1991).

1. Pathophysiology of Insulin-dependent diabetes mellitus (type I)

Insulin-dependent diabetes mellitus(IDDM) is clearly associated with an absolute deficiency of insulin secretion.The insulin deficiency is easily demonstrable when one measures circulating insulin levels in either the basal or stimulated state. The loss of insulin secretion in IDDM appears to result from an autoimmune process which is directed at the insulin producing beta cells of the pancreas and ultimately leads to their destruction and the development of the syndrome. This autoimmune process itself is probably triggered by some environmental factors in a genetically susceptible individual. Exactly what these factors are is unknown, but animal studies suggest viruses or toxins as likely candidates (Bottazzo, Florin-Christensen and Doniach, 1974). The first clue that an immune mechanism may be involved in diabetes came from the association between IDDM and other endocrine deficiencies

of autoimmune etiology, such as those of the adrenal or thyroid glands. Patients with IDDM were also found to have a remarkable increase in the prevalence of other specific autoantibodies in their sera (Christy , Deckert and Nerup, 1977).

The National Institutes of Health Diabetes Data Group recommened diagnostic criteria for insulin-dependent diabetes, the onset primarily occurs among young individuals, however, it should be recognized that IDDM can be contracted at all age. Most patients have a history of polyuria, polydipsia, polyphagia, and weight loss. These symptoms often have an abrupt onset in children and a more insidious onset with increasing age. Girls often have monilial vaginitis. The classic ketoacidosis of diabetes including air hunger, rapid (Kussmual) respiration, acidosis, dehydration, vomiting, hyperglycemia, glucosuria, Ketonemia and ketouric may be seen at the initial presentation (Lernmark, 1991).

2. Pathophysiology of noninsulin-dependent diabetes mellitus (type II).

Noninsulin-dependent diabetes mellitus (NIDDM)is by far the more common form of the disease, but its pathogenesis remains even less clear and more controversial than that of IDDM. NIDDM is associated with obesity in more than 80 % of patients, suggesting the possibility that this type of diabetes may be due to a disordered mechanism of appetite regulation or energy expenditure. Finally, and importantly, in contrast to the patients with IDDM, type II

diabetic have considerable preservation on the beta cell mass and often secrete substantial quantities of insulin into the circulation. This has led to the idea that NIDDM there is resistance of the peripheral tissues to respond to insulin. (Maclean and Ogilive, 1975)

In the presence of moderate fasting hyperglycemia (>200 mg/dl) insulin responses to glucose are greatly diminished in NIDDM. Early in its natural history the insulin secretory defect and insulin resistance may be reversible by treatment (eg. weight reduction) with normalization of glucose tolerance. The typical chronic complications of diabetes, seen in IDDM, namely macroangiopathy, neuropathy and cataracts, are seen in NIDDM as well. (Scarlett, Gray and Griffin, 1982)

Cardiovascular complications in diabetes mellitus

Diabetes mellitus is a chronic metabolic syndrome charecterized by hyperglycemia, a relative or absolute deficiency of insulin, and deranged metabolism of carbohydrates, fats and proteins. As a function of time, this chronic metabolic abnormalities will lead to the developments of various chronic complications, namely macroangiopathy, cardiomyopathy, neuropathy, and nephropathy.

1. Diabetic cardiomyopathy

In stead of the metabolic coma, nowadays cardiac disease have become as the main cause of death in insulin-dependent diabetes mellitus (IDDM). The traditional point

of view believed that diabetic heart disease was simply the result of accelerated atherosclerosis in the coronary arteries. In fact large epidemiological studies demonstrated that atherosclerotic changes are found more frequently among diabetic than non-diabetic subjects (Kannel, Hjortland and Castelli, 1974). More recently Ledet et al. (1979) hypothesized that the existence of cardiac diseases particular to diabetes as a result and combination of microangiopathy, macroangiopathy, neuropathy and metabolic dysfunction. Non invasive studies using systolic time intervals and echocardiography have investigated the relationship between glucose metabolism and myocardial contractility in diabetes. From a clinical point of view, it is well-known that the acute metabolic status of diabetic patients admitted with myocardial infarction influences the short and long-term prognosis since congestive heart failure is more frequent in those patients with high blood glucose concentrations (Kannel, Hjortland and Castelli,1974).

In most of the reports the mortality after myocardial infarction in diabetic patients shows a two-fold increase. Elevated blood glucose levels are frequently associated with myocardial infarction of a large area and usually it is suggested that hyperglycemia at admittance most probably indicates the pre-existence of diabetes mellitus. On the other hand, the incidence of cardiogenic shock and the mortality rate are also related to the patterns of blood glucose and glycosylated hemoglobin A1c showed by the patient when admitted to the coronary care

unit. Thus several epidemiological, clinical and prospective studies tend to support the conclusion that the main clinical cardiac complication in diabetes, with or without myocardial infarction, consists of decreased contractility of the left ventricle (Gotzsche, 1986). The existence of a diabetic cardiomyopathy was first suggested by Rubler et al. (1972) based on postmortem findings in four diabetic adults who suffered form congestive heart failure in the absence of atherosclerotic, valvular, congenital, hypertensive, or alcoholic heart disease. All patients demonstrated electrocardiographic evidence of left ventricular hypertrophy and at autopsy was found in association with myocardial enlargement, hypertrophy, and fibrosis. Further support for the existence of a diabetic cardiomyopathy was provided by Hamby, Zoneraich and Sherman (1974) who noted an increased incidence of diabetes in patients with idiopathic cardiomyopathy. Autopsy findings of four diabetic subjects revealed patent epicardial coronary arteries, but pathologic changes compatible with diabetic vasculopathy were noted in intramyocardial vessels. In another study, Regan, Lyons and Ahmed et al. (1977) subsequently described the angiographic and hemodynamic finding in a group of 17 patients had experienced episodes of congestive heart failure despite the absence of coronary disease on angiographic. Hemodynamic findings included an elevation of left ventricular end-diastolic pressure and a reduction of both stroke volume and ejection fraction. Ventricular compliance was also found to be significantly diminished.

Airaksinen et al. (1984) studied 36 young insulin-dependent women free of clinical cardiac disease on hypertension by digitized M-mode echocardiography suggested that diabetic subjects with severe microvascular complication had thicker left ventricular walls and smaller end-diastolic diameters and stroke volumes compared with healthy control individuals. In experimental studies, the majority of experimental work has been performed in animals with drug-induced diabetes mellitus. Regan, Ettinger and Kahn et al. (1974) utilized the alloxan diabetic dog model in a pioneer study. Hemodynamic studies after 11 months revealed diminished left ventricular end diastolic volumes and stroke volumes in diabetic dogs, this diminished left ventricular compliance was attributed to the accumulation of periodic acid-schiff (PAS) positive material (presumably glycoprotein) in the interstitium. Haider, Yeh and Thomas et al. (1981) studied in diabetic rhesus monkeys, two interesting observations in these studies. First, levels of triglyceride and cholesterol were elevated in the left ventricle despite normal serum concentrations, implicating abnormal myocardial intracellular cholesterol metabolism. Second, acute ischemic produced by coronary artery occlusion resulted in a markedly elevated left ventricular end diastolic pressure in diabetic animals compared with control animals. In a later study using chronic diabetic dogs 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

functions. (Palik et al., 1982) Chronically diabetic rats show similar alteration in cardiac performance. Relaxation as well as the velocity of circumferential shortening is impaired. Similary, cardiac output was reduced in diabetic rats utilizing isolated perfused heart techniques. Charles et al. (1985) studied the effect of experimental diabetes on cardiac function and ultrastructural in rats that had been diabetic for 6 to 24 weeks. Electron microscopic analysis of ventricular myocardium revealed increased lipid deposition from 6 to 24 weeks of diabetes. A metabolic basis of cardiac dysfunction in diabetes has been recently hypothesized by Teagtmeyer and Passmore (1985). Diabetic subjects with poor metabolic control often show elevated circulation free fatty acid (FFA) and Ketone body concentrations. The net result of these metabolic abnormalities is an increased intracellular content of triglycerides, FFA, and glycogen. These data are compatible with the hypothesis of a metabolic basis for the cardiac dysfunction in diabetes, suggesting that an excessive delivery of lipid substrates to the heart can impair the carbohydrate utilization rate in the Krebs' cycle of IDDM patients, possibly leading to a reduced ATP production. From a more general point of view these findings suggest that strict metabolic control could be important in IDDM subjects not only to achieve satisfactory normal glucose and lipid patterns, but also to obtain a normal left ventricular pump capacity.

The one interest cause of heart failure in diabetes mellitus studies by Patumraj et al. (1992) demonstrated

that microvascular abnormality might be a major risk factor for heart failure in long-term insulin-dependent diabetic patients. This study using intravital fluorescence microscopy and digital video image analysis, the extravasation of fluorescene isothiocyanate 70,000 molecular weight in isolated arrested hearts of streptozotocin-treated rats and their aged controls. The comparison of both transport parameters showed that the epicardium changed significantly in the 15 to 16 week streptozotocin rats. It is concluded that the abnormality of macromolecular permselectivity was observed in diabetic hearts and might be a factor leading to the heart failure in diabetes mellitus.Siperstein et al. (1988) have reported that 33 % of all diabetic deaths due to myocardial infarction and cardiovascular accident. Coronary artery disease manifested by narrowing of the coronary arteries is thought to be the major contributor to diabetic cardiomyopathy (Stuart, Zarich and Nesto, 1989). The existence of a diabetic cardiomyopathy was first suggested by Rubler et al. (1972) based on postmortem findings in diabetic patients. They reported that autopsies of those patients demonstrated previously electrocardiographic deragement showed left ventricular hypertrophy in association with myocardial enlargement and fibrosis. However, the pathogenesis of diabetic cardiomyopathy is unknown. Several investigators have proposed that this diabetic cardiomyopathy may be occurred as a secondary effect caused by intramural coronary artery disease (Hamby et al., 1974; Kannel et al., 1974), accumulations of

glycoprotein and collagen in the myocardium (Regan et al., 1974, Regan, Ahmed et al; 1975), and for metabolic alterations within myocardial cells themselves (Haider and Ahmed et al., 1977, Colwell and Maria, 1985). Some reports also suggested that the macrovascular disease may play the importance role in diabetic cardiomyopathy (Ross, 1986; Ross and Gomset 1976; Colwell et al., 1983). Although their isno hypothesis clearly explained the diabetic cardiomyopathy. The mechanisms of both macrovascular disease (macroangiopathy) and microvascular disease (microangiopathy) in diabetic patients have been made progressively understood.

2. Atherosclerosis in diabetes mellitus

The major problem in diabetics is atherosclerosis, and this can affect the myocardium, brain and lower limbs. Recently, many investigations have interested to clarify the mechanisms of atherosclerosis in nondiabetes. One attractive sequence of events has been proposed by Ross and Gomset (1975), Ross (1986), it is likely that certain aspects of this process are enchanced in diabetes. According to Ross's theory about the pathogenesis of atherosclerosis, this process starts with monocyte adherence to the endothelium, presumably at an area of endothelial damage. Endothelium may be damaged by physical means such as trauma, by hypertension, by a variety of biochemical mechanisms including glucose, free fatty acids, and hypercholesterolemia, as well as by immune mechanisms and by drugs. Monocyte adherence may occur, and

subendothelial migration, with transformation into macrophages, then follows. A fatty streak develops, representing lipid accumulation by monocyte-derived macrophages. Macrophages may release growth factors that stimulate smooth muscle cell proliferation and migration.

A second series of events may be initiated by platelet adherence to a site of endothelial injury. Platelet aggregation results in the release of thromboxane, a potent vasoconstricting arachidonic acid metabolite. Like macrophages, platelets may release growth factors that stimulate smooth muscle cell migration and proliferation. Low density (LDL), intermediate density, and very low-density liproprotein (VLDL) may deliver cholesterol to the damage area.

Endothelial injury

The pathogenesis of macrovascular disease in diabetes is multifactorial. Endothelial injury is an early event. There are four main pieces of evidence of altered macrovascular endothelial function in diabetes mellitus : (1) increased plasma levels of the endothelial glycoprotein, Von Willeband Factor, (2) decreased prostacyclin release, (3) decreased fibrinolytic activity, and (4) decreased lipoprotein lipase activity. There are at least 15 studies of increase plasma Von Willeband Factor levels in patients with diabetes mellitus. The ability of Von-Willeband Factor that induced platelet aggregation. Studied in 2 to 4 week after streptozotocin-induced diabetes rats found that plasma Von-Willeband Factor were increased (Colwell,

Winocour and Lopes-Virells et al., 1983). Prostacyclin is an arachidonic acid metabolite that is produced by vascular endothelial cells. It is a potent vasodilator and can antagonize platelet aggregation. Studied in animal models and human subjects with diabetes mellitus found that reduced release of prostacyclin from vascular endothelium (Colwell, Lopes-Virella and Halushka, 1981).

In the cardiovascular complication of diabetic, coronary atherosclerosis is not only more prevalent, it is also clearly more extensive in diabetic than in nondiabetic patients (Robertson and Strong, 1968). Hamby, Sherman and Metha (1976) studied at coronary angiography and autopsy in patients with diabetes have a higher incidence of double and triple vessel disease. In one large autopsy study, 91 % of patients with adult onset diabetes and no known coronary heart disease had severe narrowing of at least one major coronary artery and 83 % had severe two-or three vessel involment. From the autopsy study, diabetic patients who died of coronary artery disease had more stenosis of the arteries nondiabetic patients (Waller, Palumbo and Roberts, 1980)

3. Renin-angiotensin system interactions in cardiovascular complications.

It is apparent that process of accelerated atherosclerosis and myocardial dysfunction in diabetes mellitus is complicated. Glycemic control may affect certain aspects of this process, including endothelial and platelet function, quantitative and quanlitative

alterations in lipids and lipoproteins, and macrophage-lipoprotein interactions. One factor may accelerated atherosclerosis and myocardial dysfunction in diabetes mellitus that is renin-angiotensin converting enzyme. (Lieberman and Sastre, 1980). Schernthaner et al. (1984) showed sporadic raised activities in serum angiotensin-converting enzyme (ACE) and 14 % presented persistent raised serum ACE, confirming the report of Lieberman that a representative number of diabetics showed the raise of ACE. Funakawa et al.(1983), Valentovic, Elliott and Ball (1987) studied in the diabetic rats and showed the same results as previous studies that diabetic rats also had the increase of serum ACE activity. The mechanism for raised activity in serum ACE in diabetic remain unclear. However, one interesting about the raised serum ACE in diabetic is ACE catabolizes the conversion of angiotensin I (Ang I) to angiotensin II (Ang II). Since diabetes mellitus increase serum ACE activity, serum Ang II levels may be elevated.

Angiotensin II (Ang II) as a vasoconstrictive and growth-promoting agent, appears in contribute to the development of atherosclerosis. Ang II is a mediator of hypertrophy in vascular smooth muscle cells. It has been demonstrated to induce expression of the oncogene and platelet-derived growth factor (PDGF). PDGF results in both hypertrophy and proliferation of vascular smooth muscle cells (Geisterfer, Peach and Owens, 1988). Ang II may affect endothelial cells, althoug this is less well established than its effect on vascular smooth muscle cells. Ang II has been suggested to enchance endothelial cell

growth (Bagby and Holden, 1988).

Left ventricular hypertrophy (LVH), is now recognized as a risk factor for atherosclerotic coronary artery disease (Levy et al., 1990). In diabetic patients demonstrate left ventricular dysfunction with lower cardiac output, lower stroke volumes, a prolonged pre-ejection period and shortened left ventricular ejection time (Zorich and Nesto, 1989). In one study, the altered left ventricular compliance suggested a restrictive cardiomyopathy (Hamby et al., 1974). Diabetic animals also demonstrated that the rate of cardiac contractility was reduced and there was relaxation abnormality in the absence of atherosclerosis (Schaffer et al., 1989). LVH does not usually occur in diabetes unless hypertension is present. However, in the presence of diabetes, myocardial damage from hypertension appears to be accelerated and Ang II may act additionally as a hypertrophic factor for the myocardium (Baker and Aceto, 1990). In the recent study demonstrated that ACE-inhibitors prevent the development of LVH in animal models of hypertension and that in humans and animals with established hypertension ACE-inhibitor induce regression of LVH (Pfeffer et al., 1988). Interestingly, ACE-inhibitor was experimentally showed to have cardioprotective effects, such as, it appeared to limit myocardial infarct size, attenuate left ventricular dilatation and hypertrophy. Recently, the cardioprotective effects of ACE-inhibitor are very well documented in the reduction of coronary vascular resistance, and increasing of myocardial blood flow associated with blunting of Ang II formation.

By contrast, several investigations reported that ACE-inhibitor could suppress the vascular response to injury by interrupting the conversion of Ang I to Ang II, and thus this supression mechanism could result in preventing smooth muscle cell hypertrophy, proliferation and matrix protein synthesis (Ert et al., 1982; Hock, Ribeiro and Lefer, 1985).

From the points of view that ACE-inhibitor could improve cardiac performance including increased cardiac contractility and preventing vascular smooth muscle-cell proliferation, the idea is that ACE-inhibitor may be used as a preventor of cardiovascular complications in diabetes mellitus. In this investigation, STZ-rats were used as diabetic model to study the changes of cardiac functions and effects of ACE-inhibitor on the changes during the cause of experiment, 8-16 weeks.

Therefore, the objectives of this study are :

1) To study the changes of cardiac functions related to morphological examinations in 8-16 weeks STZ-rats

2) To study the effects of angiotensin-converting enzyme inhibitor (ACE-inhibitor) on cardiac functions and coronary arterial structure in diabetes mellitus.