# EFFECT OF SOME A.C.E. INHIBITORS ON DIABETIC MICROALBUMINIURIA

**THESIS**

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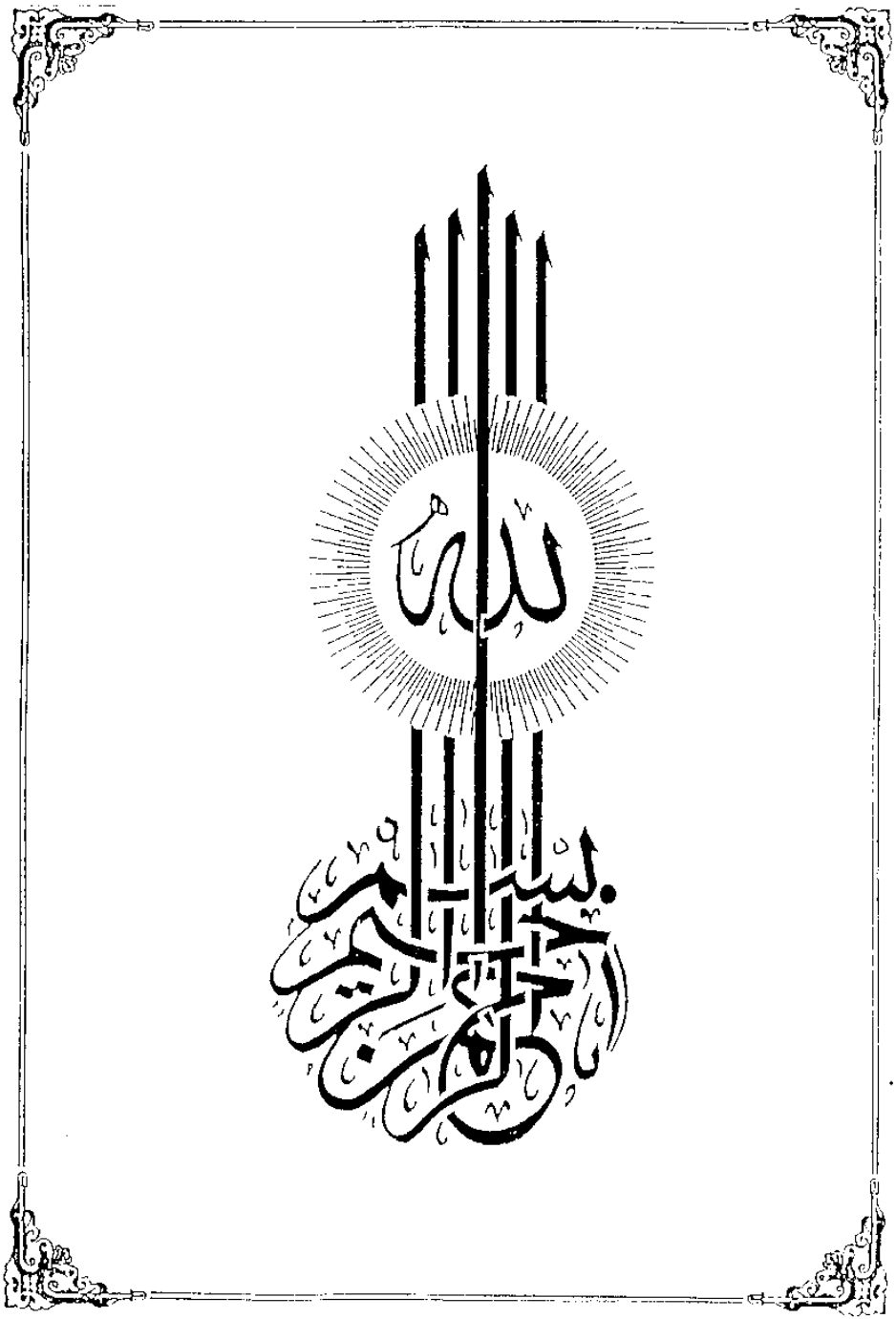

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## INTRODUCTION:

Based on retrospective studies from the 1930s to the 1960s, it has been frequently stated that diabetic nephropathy affects 30 to 35% of patients with type I diabetes, although recent evidence suggests that its incidence is decreasing. The clinical course of established diabetic nephropathy has also improved recently. For instance, the five year survival rate of patients with persistent proteinuria has increased from less than 20% before 1970 to approximately 50% in the last 20 years.

Although improved glycemic control may have played a part, a major reason for the apparent change in the natural history of diabetic nephropathy is likely to be earlier and more effective antihypertensive therapy.

In any given patient, it is not easy to determine the relationship between diabetic nephropathy and hypertension which theoretically could be cause-effect, association or effect-cause. Longitudinal studies performed in Denmark have shown that incipient diabetic nephropathy generally precedes the onset of hypertension in type I diabetic patients and cross sectional studies have also shown that a small rise in blood pressure is a feature of incipient nephropathy.

The aetiology of diabetic nephropathy remains unclear. Nevertheless, it is of urgent importance to detect the patients predisposed to this complication, as it is well known that early measures can modify the course of the disease .

# AIM OF THE WORK

The purpose of the present study is to compare the effect of some A.C.E. inhibitors on diabetic microalbuminuria to determine if there is evidence for a specific effect of them on decreasing microalbuminuria in diabetic patients.

3 members of A.C.E. inhibitors will be under comparison in this study which are

1- Captopril in a dose of 12.5 mg/day

2- Perindopril in a dose of 2.0 mg/day

3- Lisinopril in adose of 5 mg/day

# REVIEW OF LITERATURE

# WHAT IS DIABETES MELLITUS

## Historical Note :

The word (diabetes)is a Greek term and literally means (siphon). It was chosen by ancient physicians to denote copious and apparently unregulated discharge of urin i.e. (polyuria) the word (mellitus) is actually Latin and literally means : (Honeysweet) Hence (diabetes mellitus) historically was employed in reference to patients with persistent and copious discharge of sweat urin, what we would refer to as polyuria and glucosuria ***(Selby et al., 1990).***

Of course polyuria and glucosuria do not define diabetes mellitus; they merely characterize the condition and loosely reflect degree of glycemia. That the kidney itself could become structurally deranged and functionally impaired to the point or uremia in the context of diabetes mellitus was not formally recognized until 1936 when kimmelstiel and wilson reported nodular amorphous concretions in the glomeruli of patients with long standing diabetes who for the first time in history were being kept alive with exogenous daily insulin injection ***(Mogensen et al., 1984).***

Diabetes mellitus is a very common disorder with an estimated prevalence between 2 and 4 per cent in the united states. The complications of diabetes account for over 25 per cent of all new cases of end stage renal failure and over 50 percent of all lower extremity amputations and diabetes is the leading cause of blindness with approximately 5000 newly discovered cases per year additionally diabetes account : for 10 per cent of al acute hospital days ***(Nutall, 1983).***

## Evidence of genetic factors:

The evidence that diabetes mellitus is at least in part genetically determined comes mainly from studies of twins and knowledge of the frequency of the disease among relatives of affected persons.

## Twins studies:

Concerning data from twin studies it is necessary to add a word of caution. If both members of a pair of identical twins have the same trait, this does not prove that trait is hereditary since twins tend to share the same environment. It is possible they will be exposed to the same hazards; for example if one of them contracts a contagious disease such as impetigo it is more than likely that the other will also be affected; but obviously impetigo is not hereditary. If a particular trait is entirely genetically determined, then whenever one identical twin is affected the other will also be affected even if they have been brought up in different environment ***(Emery, 1986).***

One large survey showed that about 65% of identical twins were concordant whereas only about 20% of non identical twins were concordant. At the time the study was made, only some twins had completed their life spain. It is possible that concordance rates would have been higher if all twins had been followed till death. Nevertheless, the data certainly indicates that genetic factors are involved in diabetes mellitus but the fact that a significant proportion of the identical twins were discordant suggests that the genetic predisposition does not always manifest itself and that environmental influences must also be involved ***(Nance, 1979).***

## Family studies:

The Royal College of General Practitioners in London made a study of the first degree relatives (parents, offspring and; sibs) of 1307 diabetic patients and compared the results with the findings in first degree relatives of a non diabetic control group of 859 persons selected at random from the general population. With regard to the finding in the sibs the results were very interesting.

Diabetics under 30 when diagnosed are about 15 times more likely to have an affected sib than healthy persons. In contrast, diabetics over 70 at diagnosis are only about 1.5 times as likely to have an affected sib. These results indicates that there is a strong genetic predisposition in those who develop the disease when young.

In the elderly, diabetes mellitus is more the result of environmental factors, at least in a proportion of such individuals in others though perhaps the minority, genetic factors may also play a part ***(Steinberg, 1973).***

## Mode of inheritance:

Some investigators believe that diabetes mellitus is inherited as an autosomal recessive trait others contend that the disease is the result of the action of many genes (multifactors). At least a proportion of non insulin dependent diabetes is now recognized to be inherited as an autosomal dominant trait.

It seems that the major genetic susceptibility to insulin dependent diabetes in man is dictated by a gene (or genes) in the HLA region of chromosome 6 which is the linkage disequilibrium with the HLA haplotype

DR3-B8-CW7-A1. Thus a sib with this haplotype is at an increased risk of developing diabetes *(Friedman & Fialkow, 1980).*

## Classification of Diabetes:

Diabetes is usually primary, but may be secondary to other disease. Primary diabetes is subdivided into insulin dependent diabetes mellitus, also known as type I diabetes, and non insulin-dependent diabetes mellitus, also known as type II diabetes. Many find this alternative nomenclature confusing, and some explanation is needed.

The term **Juvenile Onset and Maturity Onset Diabetes** were widely used in the past. However, this classification fell out of favour when some young patient were shown to have the (mature) form of the disease, and vice-versa, making nonsense of the distinction.

Type I and type II diabetes are terms introduced many years ago by Himsworth, who predicted (long before insulin assays were available) that the former resulted from insulin deficiency and the latter from insulin resistance *(Olefsky, 1992).*

## Type I insulin-dependent diabetes mellitus (IDDM):

Type I diabetes is characterized by little or no endogenous insulin secretion. Because of the marked hypoinsulinemia; patients with this disorder usually present with the acute complications of diabetes mellitus such as polyuria, polydypsia, polyphagia, and ketoacidosis. In order to prevent ketoacidosis and death, these patients require exogenous insulin replacement. After the onset of diabetes, patient usually enter a (honeymoon phase) that may last several weeks or months during which time endogenous insulin secretion is restored and glucose metabolism may

approach normal. Unfortunately the disease invariably replaces and life long insulin is required.

The peak age of onset of IDDM is between II and I3 years, coinciding with the onset of puberty but type I diabetes; can begin at any age, including in the elderly. Patient with this disorder are usually of normal weight or thin. Specific HLA phenotype (DR3, DR4) occur at a much greater frequency in patient with IDDM than in the general population.

The etiology of IDDM is unknown. A leading hypothesis is that a viral illness or another yet unspecified initiating event may damage the beta cells of the pancreas, followed by a slow auto immune destruction of the remaining beta cells in susceptible individuals.

Anti-islet cell and anti-insulin antibodies may be detected in individuals several years prior to the onset of diabetes followed by a slow deterioration in glucose tolerance which finally results in the abrupt onset of the disease; antibodies against the islet cells of the pancreas are present as high as 90% of type I diabetic patients; but they diminish in frequency to 5 to 10 percent after 20 years. This auto immune hypothesis would also account for the increased risk of developing diabetes in individuals; with certain HLA genes, because the genes that control the immune response are located on the sixth chromosome close to the HLA loci ***(Olefsky, 1992).***

## Type II Non-Insulin Dependent Diabetes Mellitus (NIDDM):

Type II diabetes is much more common than IDDM (approximately 10 cases of type II diabetes for every case of type I) and usually has its

onset after age 40. Between 50 and 90% of the patients with NIDDM are overweight. Some patients are asymtomatic and an elevated plasma glucose is noted on routinely laboratory study. In other patient, polyuria, polydypsia, weakness, fatigue or weight loss brings the patient to the attention of the physician. More rarely patients with NIDDM first seek medical care because of the complications of long-standing diabetes.

Plasma insulin levels are relatively decreased in patients with NIDDM but are not as severely reduced as in type I. In some individuals, plasma insulin levels may be within the normal range or even elevated. Patients with NIDDM almost always secrete decreased amounts of insulin, however; following oral glucose challenge. Because insulin deficiency is not marked, ketoacidosis is not common in NIDDM unless a stress full even such as myocardial infarction or infection is superimposed.

In addition to the abnormalities of insulin secretion, patients with NIDDM are also resistant to the action of insulin. This insulin resistance is due both to a decrease in insulin binding to its plasma membrane receptor and to post receptor defect in insulin action. Thus, both a decrease in insulin secretion and impaired insulin action contribute to the hyperglycemia observed in NIDDM. At this time the relative importance of these abnormalities in producing the impaired glucose metabolism is unclear.

While this classification is convenient and useful, there are some patients who are difficult to place in a specific category. Additionally patients will, on occasion, progress from a type II form of diabetes to a type I. It is likely that with each category, there are multiple subtypes that have not yet been recognized and defined ***(Emery, 1986).***

**Secondary Diabetes:** This type of diabetes is comparatively rare. For example destruction of the pancreas secondary to pancreatitis; cushing syndrome & acromegaly are other examples.

Comparison of type I and type II Diabetes Mellitus:

| | Type I | Type II |
|---|---|---|
| + Synonym | IDDM | N IDDM |
| | Juvenile onset | Adult onset |
| + Ag of onset | Usually < 30 | Usually > 40 |
| + ketosis | Common | Uncommon |
| + Body weight | Nonobese | Obese (50-90%) |
| + Endogenous insulin secretion. | Sever deficiency | Moderate def. |
| + Insulin resist. | Occasional | Almost always |
| + HLA association. | DR3, DR4 | None |
| + Identical twins. | < 50% concordant | Almost 100% |
| + Islet cell a ; b. | Frequent | Absent |
| + t. t.t. è insulin | Necessary | Not required |