DIASTOLIC ABNORMALITIES IN YOUNG ASYMPTOMATIC DIABETIC PATIENTS ASSESSED BY PULSED DOPPLER ECHOCARDIOGRAPHY

Thesis Submitted For Partial Fullfilment

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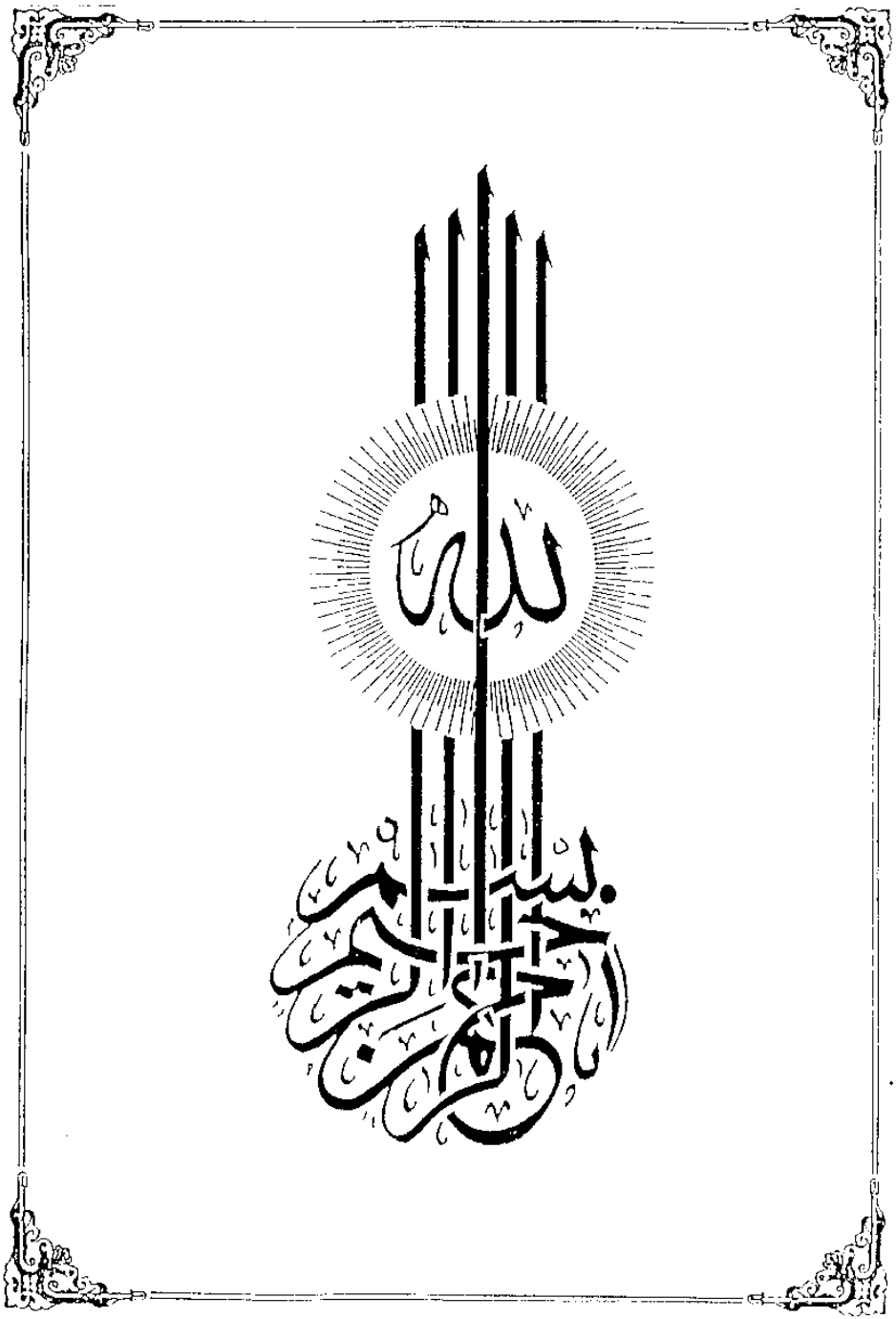

C O N T E N T S

Introduction and Aim of Work

I N T R O D U C T I O N

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Diabetes mellitus is a clinical syndrome characterized by hyperglycaemia due to diminished effectiveness of insulin. It is a common metabolic disorder of high prevalence allover the world. Its distribution throughout the world is heterogenous and the types of diabetes, together with its clinical component, are identical in all regions.

In industrialised countries, diabetic patients are ferquently obese, but in under-developed countries they are thin. Diabetes is an ubiquitous disease affecting to varying degrees, neonates ,children, pregnant women, adults and elderly. The lack of insulin whether absolute or relative affecting the metabolism of carbohydrates, protein, fat, water and electrolytes (Keen et al.,1981).

Insulin-dependant diabetes in young subjects essentially in subjects with DR w3, DR w4, B8 and/or B w15 histo-compatibilty genes. These subjects have a predispostion to develop immune disease such as hyperthyroidism, prenicious anaemia and/or Addison's disease (Hoet, 1988). In young diabetics, the beta cells present an immune reaction, which results, certain sings of regeneration, in specific destruction and depletion of these cells (Eisenbarth et al.,1988). This reaction may be influenced by immuno-suppression induced for example,by administration of cyclosporin (Stiller, 1984).

Under these very specific conditions, relatively temporary remission may be obtained. Non insulin-dependant diabetes also demonstartes lesions in the islets of Langerhans. The mass of beta cells may be reduced particularly in the presence of amyloid deposits consists of fibrils containing elements of the B chain of insulin and calcitonin-gene-related protein (CGRP). The element of this neuropeptide, called Islet Amyloid Polypeptide (IAPP), are present in the islets of diabetic cats , primates and human subjects.

The intrapancreatic nerves and neuroepithelial bodies also contain these elements, which are very similar to these affect the central nervous system due to infection with slow virus such as in Kuru or Creutzfeld-Jorob disease (Hoet, 1988). Thus the role of slow viruses in Type II diabetes has been proposed, but remains to be elucidated. The presence of insulin antibodies has also been demonstrated in Type I insulin dependant diabetic patients before initiation of insulin treatment (Palmer et al., 1983). These antibodies may be present in large percentage of Type I diabetics. Since cytoplasmic islet - cell antibodies are not specific to beta cells and cell surface islet - cell antibodies are present in a high percentage of non - diabetics (Plamer et al. ,1983), insulin may prove to be superior to islet - cell antibodies.

The presence of these antibodies only indicate that is an immunologic abnormality but it does not predict when diabetes will develop.

Eisenbarth has divided the natural histroy of Type I diabetes into six stages :-

Stage I : Genetic susceptibility

Stage II : Presence of a triggering factor

Stage III : Active immunity

Stage IV : Progressive loss of glucose stimulated secretion

Stage V : Overt diabetes

Stage VI : Complete beta cell destruction

(Eisenbarth et al .,1986)

Usually, the diagnosis of Type I diabetes is made at stage V, of overt diabetes , when extensive beta cell destruction has been already occured . The insulin treatment allows the patient to have a normal and productive life and prevents mortality from diabetic coma. However, there is a major current unsolved problem in diabetes managment which is the development of diabetic chronic complications . In the first 10 to 15 years after the diagnosis of Type I diabetes , the majority of patients do not present these complications . But thereafter , microangiopathy , macroangiopathy , and neuropathy inevitably begin and that means the start of devastation .It has not been possible to prevent these complications and their appearance

not only means a deterioration in quality of life but also diminishes life expectancy . Thus the prognosis of Type I diabetes is still regarded as very unsatisfactory .

Recently , there is increasing evidence that diabetics have abnormalities of left ventricular function in absence of clinical heart disease (**Ahmed et al . , 1975** and **Sanderson et al . , 1978**) . Whether this results from small vessel disease of the myocardium , the metabolic effect of diabetes , or coronary artery disease is unknonwn , but Framinghan study (1979) showed that diabetics suffered an incidence of heart failure in excess of that predicted from atherogenic risk factor .

The existance of diabetic cardiomyopathy was first proposed by rubler et al in 1972 on the basis of post mortum findings . Hamby et al in 1974;then reported a significantly increased fequency of diabetes in idiopathic cardiomyopathy unassociated with large coronary artery disease . Subsequently , abnormalities in both systolic and diastolic performance were demonstrated in animal (**Regan et al . , 1974**) and human (**Ahmed et al . , 1977**) studies . Recently , increasing alternation has been focused on the importance of left ventricular diastolic dysfunction in producing congestive heart failure with intact systolic function (**Doudherty et al . , 1984** and **Soufer et al., 1985**). Diastolic abnormalities have noted precede systolic dysfunction in many instances (**Aroesty et al . , 1985**) , and

many herald subsequent progressive deterioration .

An Austrian professor of mathematics and geometry Johann Christian Doppler (1803-1853) , is generally credited with the intial description of what was come to be known as the "**Doppler effect**". His article , published in 1842 (**Huntsmen et al . ,** 1983), established the relationship of ferquency to velocity . Dr. Doppler applied the principle to shifts in red light from double stars , but not directly to sound . Later in the same decade Dr.Bays Ballot applied this principle to sound . Following the second warld war , Satomur first reported cardiac evaluation using Doppler principle(**Labovitz et al ., 1985**) . Accordingly , the first Doppler cardiac evaluation followed the initial imaging work by Edler by only 2years (**Lewis et al .,** 1984) . During the next several years , the Doppler principle was used as an invasive method for monitoring the blood flow in animals by implanted Doppler transducers (**Schuster et al .,1984**). The invasive technique developed by Franklin , Baker and Rushmer were eventually extended to humans (**Kosturakis et al ., 1984**). During the later portion of 1960s , Doppler was transformed into a non invasive modality and was used by several investigations groups including those led by Edler , Kalmanson and Peronneau but the invasive phase was reintroduced in 1972 by Benchimal and co-workers who utilize a catheter tip Doppler transducer to monitor velocities during the course of cardiac catheterization . Combined expertise of Donald Baker

(University of Washington) and Ralph Astengo (President of a then felding Doppler company , advanced Technology Laboratories) , resulted in the first commercial Doppler instrumentation in 1975-1976 . In 1978 Gessert and Taylor made a major technologic breakthrough by combining two - dimensional echocardiography with fast fourier analysis of the pulsed Doppler signal . This combination provided linear signal analysis and a conveniant method for pulsed Doppler sample volume placement by two - dimensional echocardiography guidance Although the time was ripe for development of clinical Doppler echocardiography , general clinical usage did not start until approximately 1982 since that time Doppler has been incorporated into cardiac ultrasonic examination on regular basis in many non invasive laboratories.

AIM OF THE WORK

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The existance of diabetic cardiomyopathy has been proposed because evidence has accumulated for the presence of subclinical impairment of left ventricular diastolic function in diabetic patients in absence of ischaemic , valvular or hypertensive heart disease (Zarich et at . , 1988).

This work is aiming at early detection and assessment of the degree of left ventricular diastolic dysfunction in asymptomatic insulin - dependant diabetic patients evaluated by pulsed Doppler echocardiography.

Review of Literature

REVIEW OF LITERATURE

1- Changing Concepts of Diabetes Mellitus

Definition

Diabetes mellitus is a diagnostic term applied to a constellation of anatomic and biochemical abnormalities which have in common , as part of syndrome , a disturbance in glucose homeastasis , which is secondary to diminished insulin action , due to its decreased availability, or effectiveness , in varying combination . It is however , difficult to produce a single binding defention because of heterogeneous aetiologies of diabetes (Chaill., 1982 , Alberti & Hockaday .,1983) . Diabetes may present with acute symptoms that include thirst , polyuria and unexplained weight loss "classical onset" and these can progress to life threatening ketoacidosis or hyperosmolar coma . Subacute symptoms include the above , together with prurites vulvae , balanitis , other skin infection , unusual fatigue or visual impairment .Another presentation is chronic hyperglycaemia which may be asymptomatic but is generally recognized as a predisposing risk factor specific microvascular complications , namely retinopathy and nephropathy (Welborn .,1984).

History

Description of the disease were made 3000 years ago in

Egypt . About 400 B.C.,Charak and Susrut in India noted not only the sweetness of the urine but also the correlation between obesity and diabetes , and the tendency of the disease to be passed from one generation to another through "seed" . Near the beginning of the christian era , the Romans Aretaeys and Celsus described the disease and gave it the name diabetes (=siphon) mellitus (melli=hony or sweet). Its correlation with gangrene was mentioned by the Arab,Avicenna, 1000 A.D. . The sweetness of the urine was again described by Thomas Willis (1775). Dodson, 100 years later, demonstrated that the sweetness was due to sugar and suggested it was not formed denovo by the kidney but rather that the kidney removed it from the body, a fact scientifically confirmed by the great frensh physiologist, Claude Berard, in the mid 1800's. In (1889) Von Mering and Minkowski first produced expermental diabetes by removing the dogs pancreas . Subsequently, Opie(1901), noted changes in the islets of cells of pancreas (the islet having been described by Langerhans in 1896)in human dying with disease. This led to attempts by many to prepare pancreatic extracts which could correct the deficiency ,untill Banting and Best discovered insulin in 1921 in Toronto . In (1936) the use of long acting insulin was introduced , simplifing the mangement of the insulin-reguiring diabetes, but did not provide the total solution for the diabetes and its problems. Another development, clearly less significant than that of