BLOOD SEROTONIN CONCENTRATION IN DIABETIC PATIENTS WITH PERIPHERAL VASCULAR COMPLICATIONS.

THESIS

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By

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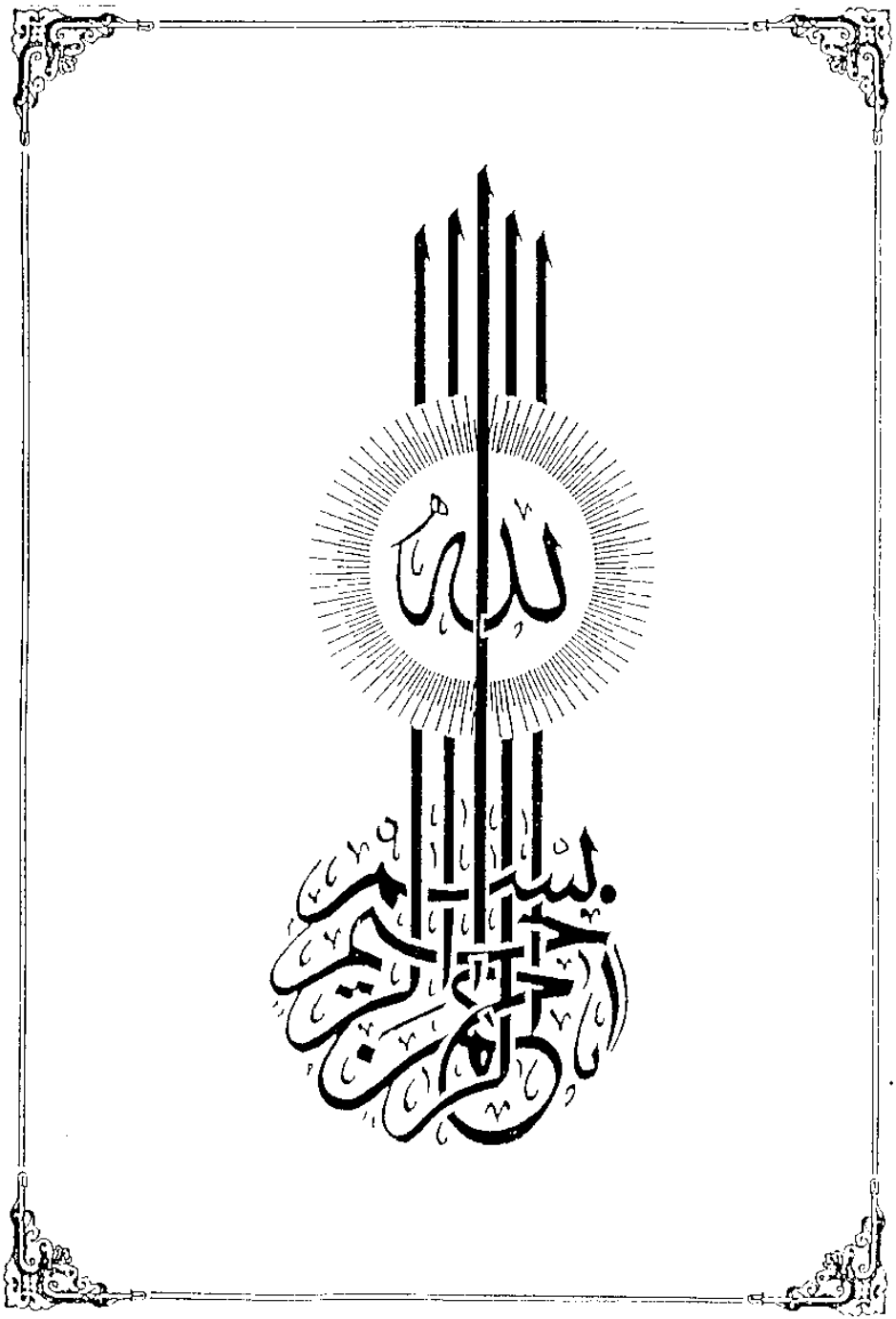

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Introduction & Aim of the Work

INTRODUCTION AND AIM OF THE WORK

The incidence of peripheral ischemia and gangrene of the foot in diabetics is over 30 times that of age matched controls. The factors responsible for its development in addition to peripheral vascular disease are small vessel disease, peripheral neuropathy and secondary infection (**Greenspan and Forscham 1988**).

Serotonin is synthesized within the chromaffin cells in the intestine. It is stored in the platelets. Once released, it can modulate vascular phase of homeostasis by causing constriction of blood vessel wall. Exogenous serotonin has complex and multiple actions on cardiovascular function. Depending on the vascular bed studied, the initial vascular tone present, and experimental condition used, the monoamine augments or reduces blood flow. Thus, the net effect of serotonin is dependent on the balance between its vasoconstrictor and vasodilator actions (**Van Nuetten 1985a**). The vasoconstrictor effect of serotonin is augmented during hypoxia, cooling, hypertension, and atherosclerosis (**Van Nuetten 1985b**). Moreover, plasma serotonin concentration is increased in cases of embolism and coronary thrombosis (**Goliano** 1985).
The forementioned data may imply that serotonin has a role in the regulation of blood flow in normal and pathological conditions.

Diabetes mellitus is associated with disturbance in platelet function in the form of increase in platelet adhesion which is the major secretaguege of serotonin in blood (**Eisenbarth and Kahn 1990**).

Based on the above mentioned effects of serotonin, it is tempting to study its possible role in peripheral vascular diseases both in diabetic and non diabetic patients with peripheral ischemia.

In this work, two groups of diabetic patients were used.The first had laboratory evidence of diabetic ischemia and the second group had foot sepsis without evidence of ischemia. Another group of non diabetic patients with peripheral ischemia of lower limbs was also included. All groups were evaluated against normal healthy controls as regards blood serotonin concentration and the state of peripheral arterial circulation in order to investigate the possible role of serotonin in these conditions.

REVIEW OF LITERATURE

DIABETES MELLITUS

Definition:

Diabetes Mellitus is a group of anatomical and chemical disorders resulting from a number of factors in which there is an absolute or relative deficiency of insulin or its function in the presence of a relative or absolute excess of glucagon.

When the insulin deficiency is extreme, these hormonal abnormalities are responsible for the catabolic cascade culminating in ketoacidosis. This disease predisposes to specific microvascular abnormalities including retinopathy, nephropathy, and neuropathy. It doubles the risk for stroke, increase the risk for heart attacks 2-3 fold and for peripheral vascular problems particularly in the feet, 50 fold. There are other problems such as lessening the resistance to infection, especially if the disease is uncontrolled (Cahill 1985).

A broader definition of diabetes is that it is a syndrome characterized by a state of chronic hyperglycemia caused by diminished insulin action (insulin deficiency or/and insulin resistance) and covering in its complete picture two categories of metabolic defects and structural damage triad:

(1) Metabolic defects:- beside hyperglycemia there is accelerated fat and protein catabolism.

(2) Structural damage triad (Long term triad):-

(a) Large vessel disease including accelerated atherosclerosis and medial calcification.

(b) Microvascular disease characterized by thickening and abnormality of function of capillary basement membrane resulting in neuropathy and retinopathy and nephropathy.

(c) Neuropathy: There are peripheral sensory and motor defects, autonomic nervous system dysfunction ,segmental demyelination and abnormalities of schwanns cells (Porte and Halter,1981).

Diabetes mellitus can also be defined as a clinically and genetically heterogenous group of disorders that have one common feature namely hyperglycemia due to deficient insulin level or effectiveness (Fajans et al.,1979). Therefore, diabetes mellitus should not be synonymous with hyperglycemia.

Classification:

The following classification is based on the recommendations of the National Diabetes Data Group (NDDG 1979), and the expert committe on diabetes of the World Health Organization (WHO 1980).

A. Diabetes Mellitus:

1. Insulin dependent D.M. (IDDM), type (1).
2. Non insulin dependent type (NIDDM) type (2).
   a. Non obese NIDDM.
   b. Obese NIDDM.
   c. Maturity onset diabetes of the Young (MODY).

The above mentioned types were named primary diabetes.

3. Other types (2ry diabetes) including diabetes mellitus associated with certain conditions (secondary diabetes).
   a. Pancreatic disease.
   b. Hormonal abnormalities .
   d. Insulin receptor abnormalities.
   e. Certain genetic syndromes.
   f. Other types.

B. Impaired glucose Tolerance (IGT).
   a. Non obese IGT
   b. Obese IGT.
   c. IGT associated with certain conditions.

C. Gestational diabetes (GDM).

D. Previous abnormality of glucose tolerance (PAGT)

E. Potential abnormality of glucose tolerance.

Based on the above mentioned facts, the classification recommended by NDDG (1979) can be modified such that the term insulin dependent and non-insulin dependent described physiologic states (Ketoacidosis prone and ketoacidosis resistent respectively) while the terms type I and type 2 refer to pathogenic mechanisms (immune mediated and non immune mediated respectively (Unger and Foster 1985).

Thus, three major forms of primary diabetes would be recognized.

1. Type I insulin-dependent diabetes.
2. Type I non insulin dependent diabetes.
3. TypeII non insulin dependent diabetes.

Category 2 can be considered as type I IDDM in evolution i.e. autoimmune mediated beta cell destruction occurs slowly with the result that there is delay in reaching ketoacidosis threshold (Foster,1990)..

The term type I has often been used as a synonym for insulin dependent diabetes (IDDM). The term insulin dependence is not equivalent to insulin therapy. Rather, the term means that the patient is at risk for ketoacidosis in the absence of insulin. This type is termed ketoacidosis prone diabetes. In reference to pathological mechanism, it can be called " immunologically mediated diabetes". It can be divided into two subgroups namely type I_a in which the patient have islet cell antibodies only transiently, at the onset of the disease. Subgroup I_b accounts for the remainder of insulin dependent diabetic patients. Those patients have islet cell antibodies that tend to persist in high titres. Associated autoimmune disorders of the thyroid and adrenal cortex occur frequently (**Greenspan and Forsham 1988).**

Type II diabetes is insulin independent, ketosis resistent and nonimmune mediated diabetes. It is subdivided into 3 categories. The first is the non obese diabetes of the young. It is considered as type I (IDDM) in evolution i.e. autoimmune beta-cell destruction occurs slowly rather than rapidly with the result that there is a delay in reaching the ketoacidotic threshold of insulin deficiency. The second category is the obese NIDDM in which hyperinsulinemia and insulin

resistance is the characteristic feature. The third category is the maturity onset diabetes of the young (MODY).

Gestational diabetes mellitus (GDM) is glucose intolerance that has its onset during pregnancy, virtually all patients return to normal glucose tolerance after parturition but they have increased risk for progression to diabetes . It is also associated with increased risk of congenital malformations.

Potential abnormality of glucose tolerance:

This class includes persons who have never exhibited abnormal glucose tolerance but who are at substantially increased risk for development of diabetes. They include :-

- The monozygotic twin of NIDDM patients .
- An individual, both of whose parents are diabetic.
- An individual, with one diabetic parent and the other with family history of diabetes.
- A mother giving birth to overweight babies (more than 4 kg). (**NDDG 1979**).

Secondary diabetes:

Secondary diabetes defines a class of patients in whom hyperglycemia is associated with another disease. In some, the pathogenic mechanism responsible for the development of glucose intolerance is will understood; in others , it remains obscure. The clinical phenotype reflects the underlying disorder. Diabetes secondary to intrensic pancreatic tissue is type I in character because insulin deficiency is the predominant lesion. Diabetes secondary to cushing's disease, acromegaly or glucagonoma is type 2 in character because hormonally induced insulin antagonism is the prominant lesion.(Shneider and Seegmilla 1985).

A large number of drugs may produce carbohdyrate intolerance or overt hyperglycemia. Only a portion of the patients who are exposed to diabetogenic drugs or to homrone excess sydnromes develop clinically significant diabetes. They already have a genetic propensity to idiopathic type I or type 2 diabetes, which renders them more vulnerable (Grenuth 1982).

Among the drugs that cause hyperglycemia are the insulin antagonizing hormones such as corticosteroids and thyroid when given in large doses for long time in