Cryoglobulinemia in Diabetic Patients

Thesis
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By
Tarek Ahmed Mahmoud El-Taib
M.B.,B.Ch.

Supervisors
Prof. Dr. Mohamed Awad Alla Mohamed Sallam
Professor of Internal Medicine
Faculty of Medicine
Ain Shams University

Prof. Dr. Moatasem Salah Amer
Professor of Internal Medicine
Faculty of Medicine
Ain Shams University

Dr. Nivene Nabil Kasem
Lecturer of Clinical pathology
Faculty of Medicine
Ain Shams University

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AIN SHAMS UNIVERSITY
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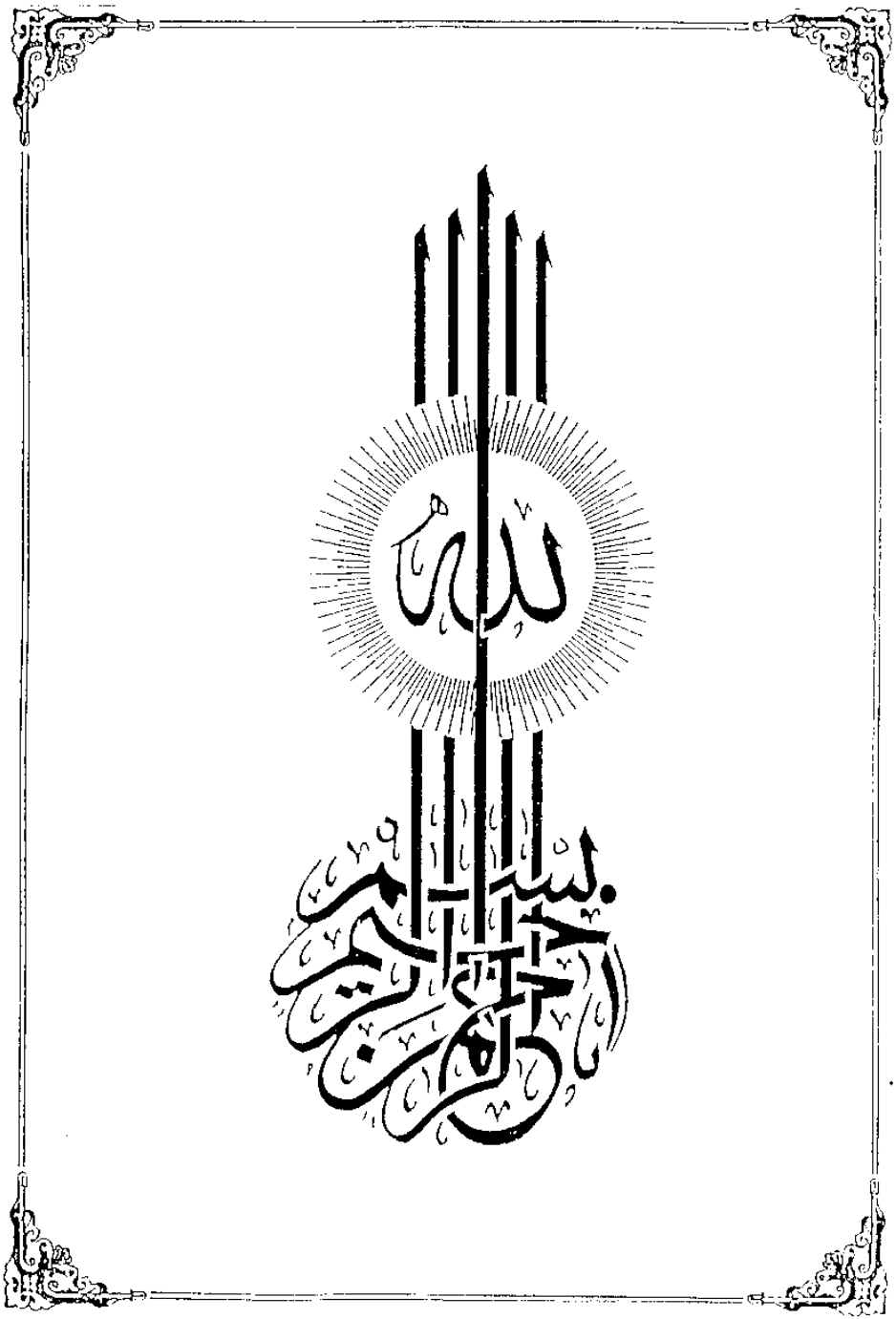
إنك أنت العليم الحكيم ﴾

صدق الله العظيم [البقرة ٣٢]



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CONTENTS

INTRODUCTION
AND
AIM OF THE WORK

Cryoglobulins are antibodies that reversibly precipitate in plasma upon cooling. They are classified into isolated monoclonal cryoglobuline (Type I). The main manifestations include hyperviscosity, cold urticaria, Raynaud's phenomenon, purpura, cutaneous vasculitis with or without ulceration or retinal hemorrhage *(Franklin, 1980).*

Mixed monoclonal cryoglobuline (Type II), the main manifestations include purpura, weakness and arthralgia, hepto and splenomegaly *(Marcellin et al., 1993).*

Mixed polyclonal cryoglobuline (Type III), The main manifestations include purpura, articular disease and Raynaud's phenomenon. These cryoglobuline are frequently associated with hematologic malignancies and lymphproliferative disease *(Franklin, 1980).*

Cryoglobulins are characterized by vascular and parenchymal deposition of circulating immunecomplexes mainly IgG-IgM cryoglobulins with rheumatoid factor activity. Nephropathy can be considered one of the most frequent complication of cryoglobulinemia *(Crespi et al., 1990).*

Patients with diabetes mellitus are prone to develope complications which may be classified as specific and non specific complications. Non specific complication include atherosclerosis, coronary artery disease, peripheral vascular diseases, cerbrovascular diseases. The specific complication arise from the combination of diabetic microangiopathy. They include retinopathy, nephropathy and neuropathy *(Toft et al., 1981).*

In type I, IDDM, the present evidence suggests that its evolution may involve an antecedent period of slowly developing autoimmune damage to the pancreatic B cells *(Gorsuch et al., 1981).* Islet - cell antibodies are usually present at the onset. Genetic factors related to histocompatibility antigen (human lymphocyte antigen) DR3 and DR4 are associated with the

predisposition to humoral or cytotoxic immune activity directed against islets tissues *(Lovise and Thomsong, 1986).*

On the other hand, Type II NIDDM disease is recognized as having strong genetic basis, as evidenced by studies of identical twins and by familial transmission of diabetes in an autosomal dominent inheritance pattern *(Fajans et al., 1978).*

Type II diabetes there is a relative lack of insolin. The isulin which is present is sufficient to prevent excessive fat metabalism, and the person is not at risk of ketosis. Itis not clear how often total insulin secretion is reduced in type II diabetes, and how often insulin secretion is relatively normal but insufficient becouse of peripheral antagonism to its action.

Measured insulin concentration are usually higher than normal, but this may be becouse of cross- reaction with insulin-related peptides, *(Fajans et al., 1990).*

The importance of presence of cryoglobuline as marker of immunological disease lead us to think about its role as aetiological factor in DM or as result of DM. So our aim, is to study the possibility of the presence of cryoglobulin in diabetic patients.

Review of Literature

IMMUNOGLOBULINS

Immunoglobulins or antibodies are glycoproteins present in gamma globulin fraction of serum.

Immunoglobulins are produced by B-lymphocytes (B-cells) or plasma cells in response to exposure to an antigen.

Structure of immunoglobulin:

A. Basic unit (monomer):

1. The basic structural unit of an immunoglobulin molecule called a monomer, consists of four polypeptide chains linked covalently by disulfide bonds.

   a. Polypeptide chains are unbranched polymers composed of amino acids.

   b. The sequence of amino acids in a polypeptide chain identifies a given protein and distinguishes it from any other molecule.

2. The four chain monomeric immunoglobulin structure is composed of two identical heavy (H) polypeptide chains and two identical light (L) polypeptide chains.

B. Heavy and light chains:

1. H chains

   a. Size: contain about 400 amino-acids, twice the number in L chain and have molecular weight of 50-75 KDa.

   b. Isotypes: Amino acid differences in the carboxy terminal portion of H-chain identify five antigenically distinct H chain isotypes.

   The H chain isotypes form the basis for the five classes of immunoglobulin molecules.

   c. Subclasses:

   H chain classes are subdivided into substances of molecules based on the greater similarity of amino acid sequence and this corresponds to immunoglobulin subclasses.

2. L chains:

   - Are of two types kappa or lambda based on their structural antigenic differences.

- All immunoglobulin classes have both K and λ chains and never contain both.
- The proportion of K to λ chains in human Ig molecules is about 3:2.
- There is no isotypic variation in K chain, however there are four distinct λ chains isotypes giving rise to four subtypes and all present in each of Ig classes hold together the four polypeptide chains in Ig molecules and are of two types:

l. The interchain bonds occurs between H-H, H-L and L-L chains.

a. H-H bonds: occurs in hinge region and in carboxy terminal protein of H chain, they vary in number from l to l5 depending on class and subclass of Ig molecule.

b. H-L bonds only one disulfide bond connects H and L chains in most Ig.

IgA_2 lacks an H-L bond.

c. L-L bonds:single L-L bonds occur in IgA_2 and occurs under pathologic conditions e.g. in Bence Jones protein.

2. Interachain bonds:

Occur within an individual chain and are stronger than interchain bonds and their number varies from 2 in L chains to 5 in H chains and divide each Ig-molecule into domains.

C. Variable (V) and constant (C) regions:

- The variable region which lies in the amino or N. terminal portion of the molecule shows a wide variation in amino acid sequence.

- The constant region in the carboxy or C terminal portion of the molecule demonstrates an unvarying amino acid sequence except for minor inherited differences.

- Certain areas within the variable regions are highly variable and often called complementary-determining

regions or hot spots and are important in structure of antigen binding site.

D. Domains

- Each immunoglobulin chain consists of a series of globular regions or domains inclosed by disulfide bonds.
- Each H chain has four or five domains, one variable region and three or four in the constant region.
- Each L chain has two domains, one in the variable region and one in the constant region.
- Domains consist of about 110 amino acid residues.

E. Antigen binding site (paratope):

- The paratope is the area of immunoglobulin molecule which interact with epitope of the antigen.
- The paratope is formed by only a very small portion of the entire immunoglobulin molecule.
- Folding of polypeptide chains brings the complement determining regions VH and VL domains into close