AMINO TERMINAL PROCOLLAGEN III PEPTIDE IN NON-INSULIN DEPENDENT DIABETES WITH HEPATOMEGALY

THESIS
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بسم الله الرحمن الرحيم

قالوا سبحانك لا علم لنا الا ما علمتنا انك أنت العليم الحكيم

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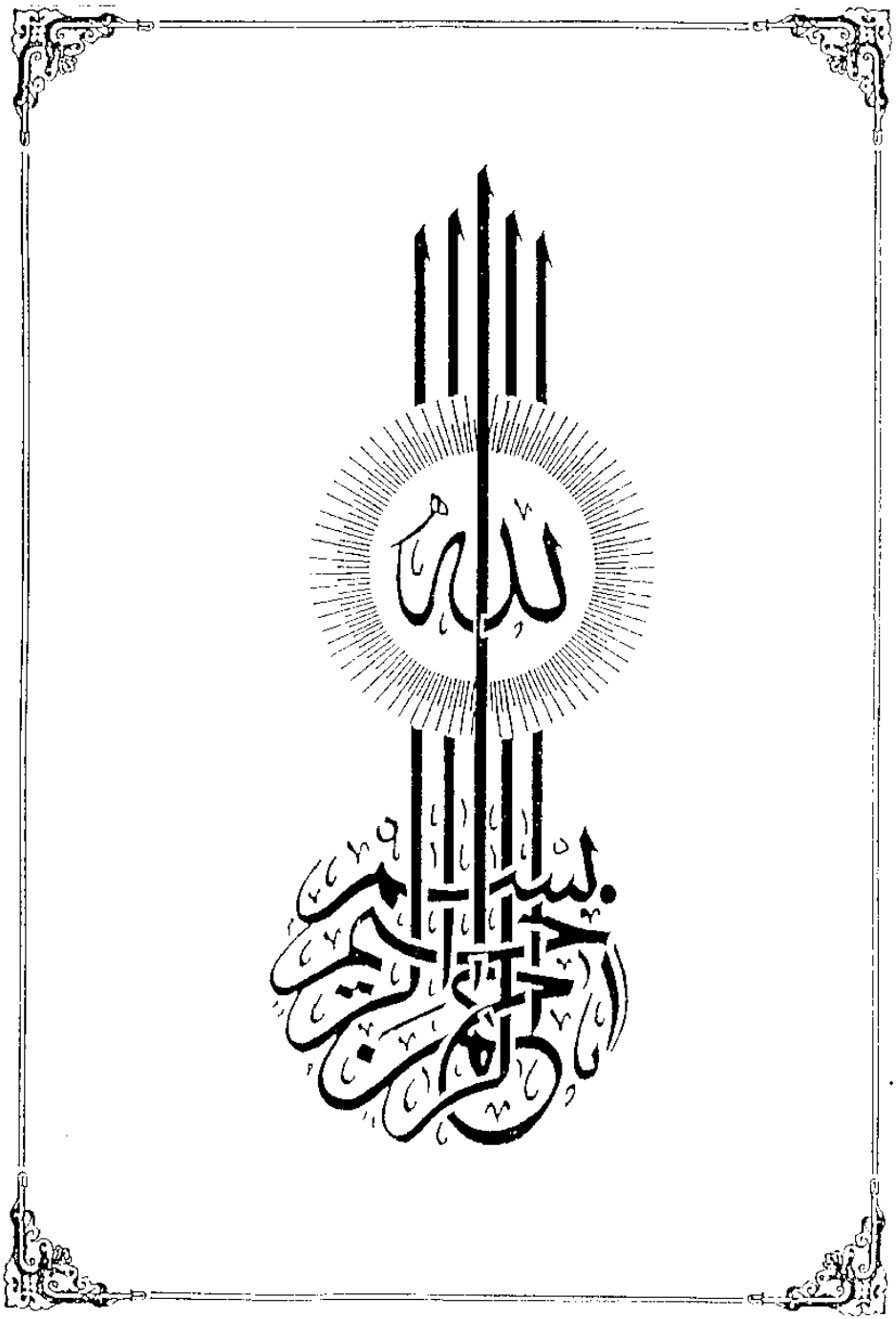

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RANDA M. BAHAA EL-DIN

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Introduction And Aim Of The Work

Hepatomegaly is a commonly associated finding in patients with non-insulin dependent diabetes. This could be attributed to fatty changes *(Falchuk et al., 1980)*. The progression to actual fibrosis or cirrhosis is still controversial.

Amino-terminal procollagen III peptide were partially set free from the procollagen molecules during the synthesis and deposition of type III collagen in the various tissue. It is also partially retained in the molecules which remain on the surface of collagen fibrils. Hence, when found in serum, it is either derived from neosynthesis of type III collagen or from the degradation of existing type III collagen fibrils. Significantly elevated serum PIIINP levels were reported in various forms of hepatitis and active cirrhosis *(Niemela et al., 1984)*.

The aim of the present study is to evaluate serum PIIINP measurements in non-insulin dependent diabetics with hepatomegaly in an attempt to clarify the possible underlying cause of hepatomegaly. In addition, study of possible associated correlations with the other conventional liver function tests will be carried out.

2

Review Of Literature

I. CONNECTIVE TISSUE METABOLISM AND HEPATIC FIBROSIS:

A] Types of Extracellular Matrix in Normal Liver:

1- *COLLAGEN*:

Collagen, the major macromolecule of connective tissue, is the most common protein in animal tissue. It provides an extracellular framework for all metazoan animals and exists in virtually every animal tissue *(Decrombrugghe, 1982)*.

a) Structure of collagen

The most definitive property of collagen molecules were their triple helix, being a coiled structure of three polypeptide subunits *(Fig. 1)*. Each polypeptide subunit or alpha chain is twisted into a left-handed helix of 3 residues per turn. Three of these left-handed helices are then wounded to a right-handed super helix to form a stiff rod-like molecule, 1.4 nm in diameter and about 300 nm long.These triple helical molecules unique to collagen are associated bilaterally and longitudinally into fibrils. Between the end of one triple helix and the beginning of the next is a gap that may provide a site for deposition of hydroxyapatite crystals in bone formation. Collagen fibrils range from 10 to 100nm in diameter and are visible by electron microscopy as a banded structure in the cellular matrix of connective tissues *(Eyre, 1980)*.

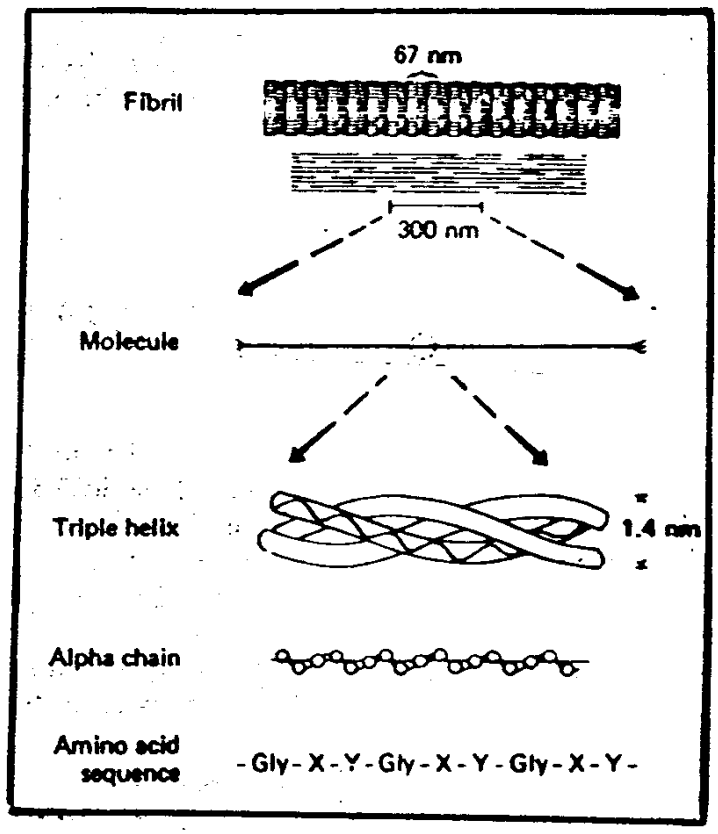

Fig. 1: MOLECULAR FEATURES OF COLLAGEN STRUCTURE FROM PRIMARY SEQUENCE UP TO THE FIBRIL (EYRE, 1980)

b) Types of collagen

The alpha helical trimer, the primary component of collagen fibrils consists of a repetitive tripeptide Gly-x-y Gly-x-y, where 'gly' is glycine, x and y are frequently proline and hydroxy proline. This helical segment varies in the amino- acid composition

of the x-y positions and the length of the segment. It may also be interrupted by non helical regions *(Miller and Gay, 1987)*. On this basis, multiple types of collagen exist; at least 12-types encoded by more than eighteen genes *(Table, 1)*. Several types are related at a molecular level and appear to have similar physiological roles *(Liau et al., 1985 and Bissell and Roll, 1990)*.

The most abundant two types of collagen namely type-I collagen and type-III are highly homologous. Their genes contain about fifty essentially identically coding sequences, separated by non-coding regions, Their expression is co-regulated even though their genes are located on different chromosomes *(Solomon et al., 1985)*.

COLLAGEN TYPES *(Bissell and Roll, 1990)*:

TYPE	MOLECULAR WEIGHT OF CHAINS	SPECIAL FEATURES
I	95,000	MOST ABUNDANT TYPE IN LIVER, BONE, SKIN AND TENDON
II	95,000	MOST ABUNDANT TYPE IN CARTILAGE
III	95,000	PRESENT IN LIVER, BLOOD VESSELS AND SKIN
IV	170,000	FOUND IN ALL BASEMENT MEMBRANES
V	185,000	PERICELLULAR AND BASEMENT MEMBRANE
VI	95,000	MAY BE PRESENT IN MICROFIBRILS
VII	140,000	MAY BE PRESENT IN ANCHORING FIBRILS
VIII	260,000	PRODUCED BY ENDOTHELIAL CELLS
IX	170,000	MINOR CARTILAGE COLLAGENS
X	180,000	
XI	125,000	
XII	100,000	

In the liver, approximately 80% of total hepatic collagen consists of equal amounts of types I & III collagen, which are confined to the portal area *(Fig. 2)*. Type-V collagen constitutes about 5 to 15% and has a general distribution around the sinusoids as well as the portal areas *(Schuppan et al., 1986)*.

On the other hand, type-IV collagen constitutes about 7% as the total and is localized to the basement membranes of lobular vessels and bile ductules. It is also present in and around the

space of Disse *(Fig. 2) (Rojkind et al., 1982)*. Type-VI collagen constitutes less than 0.1% in normal young rat liver *(Schuppan et al., 1985)*. Accordingly, interstitial liver matrix contains mainly types-I & III collagen in addition to a small percent of type-V & IV respectively. All of which except type-IV form rope-like fibrils *(Fig. 3)* that provide a tensile strength to the tissue. This is quite distinct from basement membrane matrix in which a specific type-IV collagen exists as a latice-like structure *(Fig. 3)* present at the basal pole of epithelial cells and around blood vessels at the anti luminal surface of the endothelium *(Martinez, 1984)*.

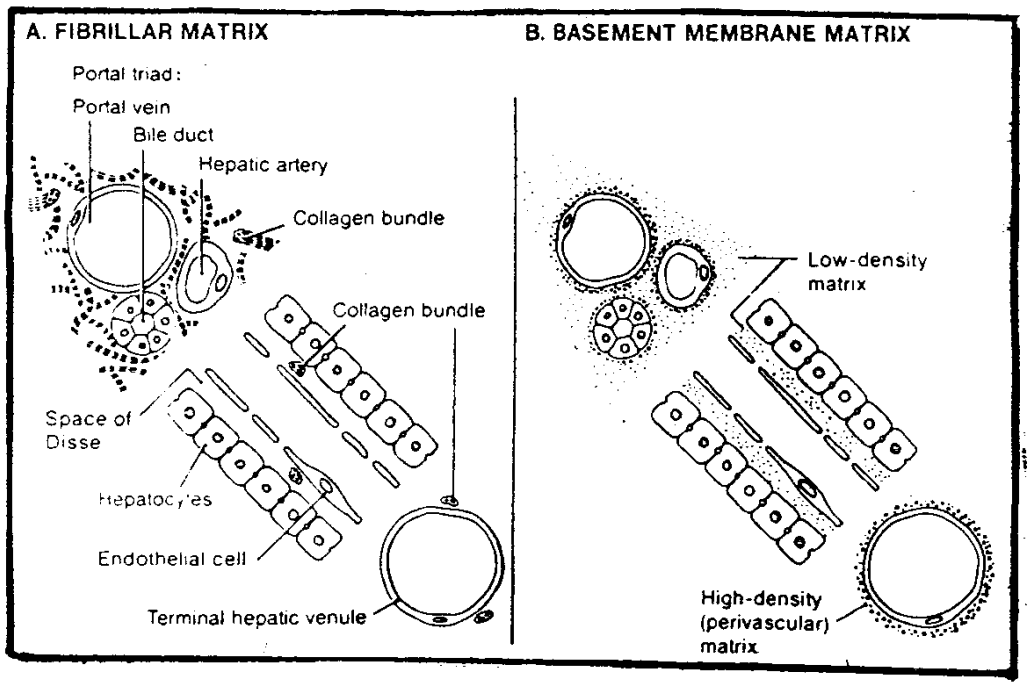

Fig. 2: LOCALIZATION OF FIBRILLAR (A) AND BASEMENT MEMBRANE MATRIX (B) IN THE LIVER (Rojkind et al., 1982)

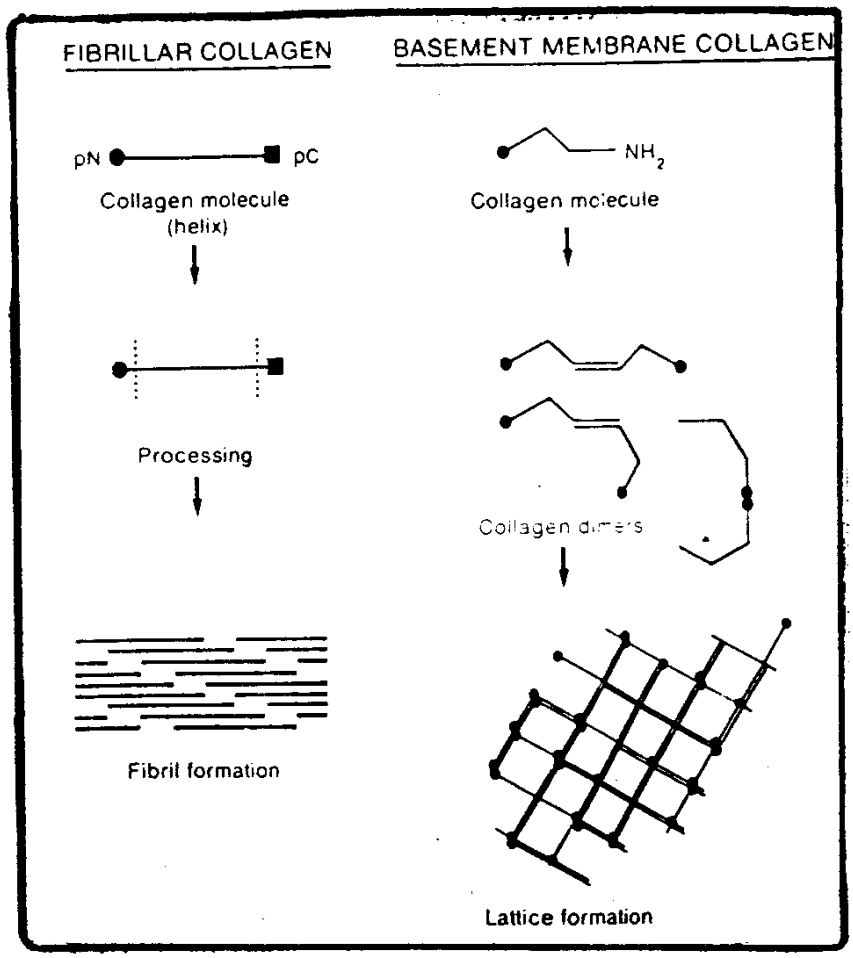

Fig. 3: FORMATION OF FIBRILS (COLLAGEN TYPES I AND III AND OF BASEMENT MEMBRANE (COLLAGEN TYPE-IV)(Martinez, 1984).

c) Synthesis of collagen:

Inspite of being an extracellular protein, collagen is synthesized as an intracellular precursor molecule that undergoes post-translation modification before becoming a mature collagen fibril *(Prockop et al., 1979).*

The initial product of collagen messenger ribonucleic acid translation is preprocollagen. The "pre" component is a short signal peptide that guides the molecule across the membrane of the endoplasmic reticulum and is then removed in this process *(Fig. 4) (Palmiter et al., 1979).*

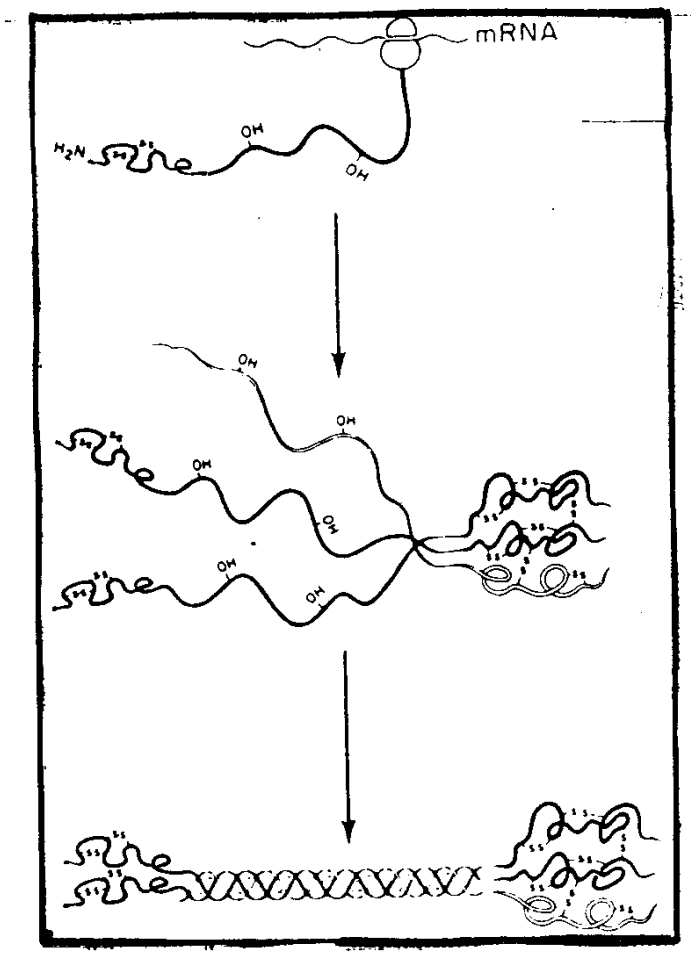

Fig. 4: BIOSYNTHESIS OF COLLAGEN (Bissell & Roll, 1990)