ESTIMATION OF SERUM LEVEL OF SOME ACUTE PHASE PROTEINS IN LIVER DISEASES

Thesis

submitted for partial fulfilment of
Master Degree in Clinical and Chemical Pathology

رسالة

By

Dr. Seif Wahib Morcos

616.0756
S.W.

Supervised by

Prof. Dr. Aida Abd El-Azim Abd El-Salam
Professor of Clinical Pathology
Ain Shams University

Prof. Dr. Laila Abd El-Aala El Shawarby
Professor of Clinical Pathology
Ain Shams University

FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY
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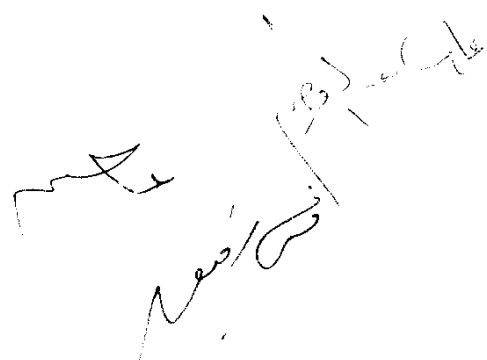

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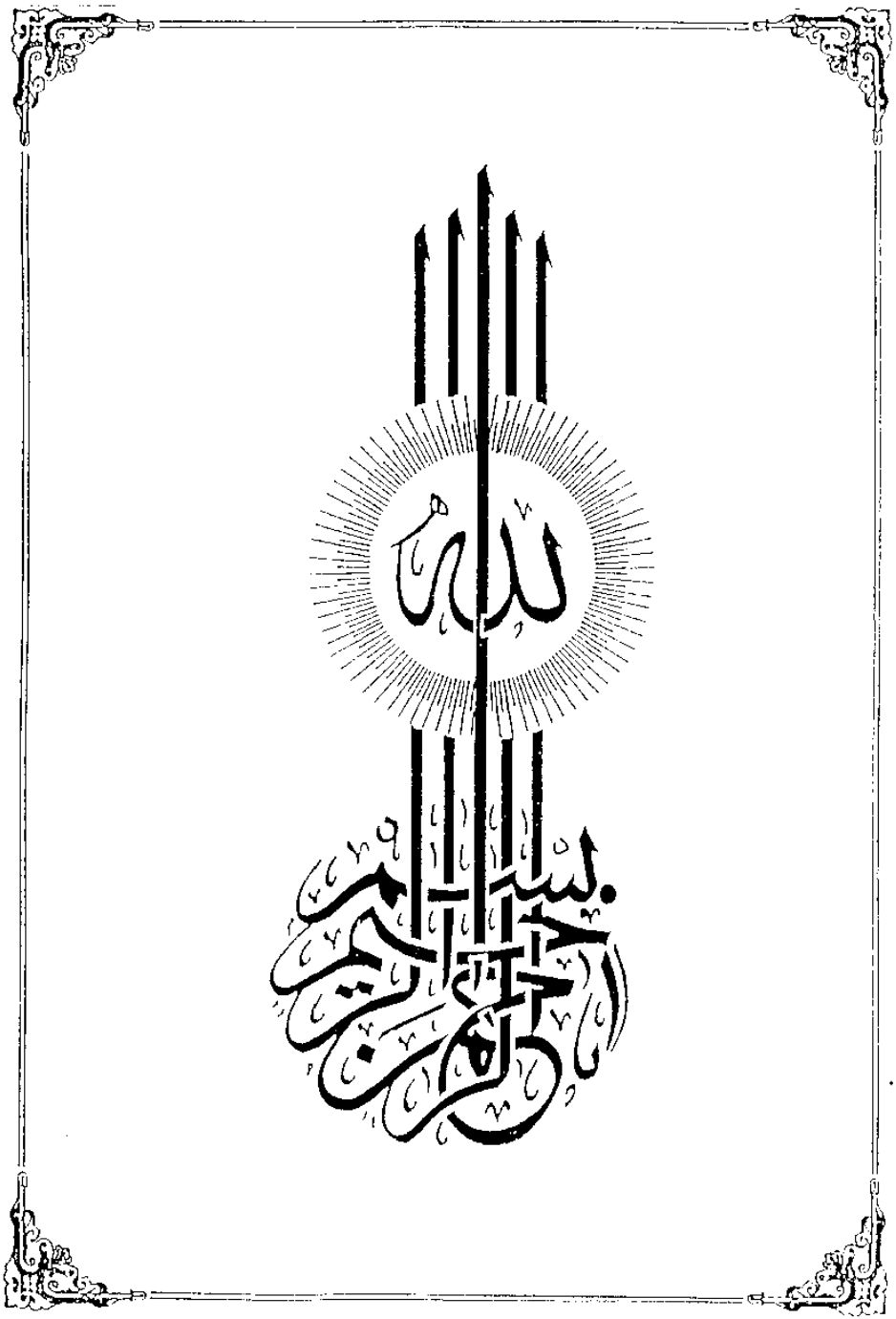

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INTRODUCTION

The proteins of acute phase response represent a vast and heterogenous group of plasma proteins which undergo marked changes in their serum levels during most acute and chronic inflammatory processes. Acute phase proteins which act as mediators, inhibitors, scavengers and immune regulators, are mainly synthesized by the liver cell triggered by cytokines as interleukin-1 which is released from activated phagocytic cells.

Previous reports on acute phase proteins in liver diseases stressed the lack of classic acute phase response and the occurrence of changes in some acute phase proteins common to the liver diseases.

AIM OF THE WORK:

Study of serum levels of some acute phase proteins in acute and chronic liver diseases with different aetiology, and to evaluate its diagnostic and follow up values.

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THE PATHOGENESIS OF THE ACUTE PHASE RESPONSE

Microbial invasion, tissue injury, immunologic reactions and inflammatory processes induce a constellation of host responses collectively referred to as the acute phase response. This response is characterized by changes in metabolic, endocrinologic, neurologic and immunologic functions, with a full spectrum of response includes dramatic increase in the synthesis of hepatic acute phase proteins (Dinarello, 1984).

Changes in the acute phase proteins serum levels may reflect the inflammatory activity of the disease processes and also serve as an indicator of silent disease and some cancers, particularly renal-cell carcinoma and Hodgkin's disease (Dinarello, 1984).

Perhaps the most fundamental event in the initiation of the acute phase response in the production of mediators which induce both laboratory and clinical features of the acute phase response, these mediators are mainly interleukin-1 and tumor necrosis factor-alpha (TNF). Monocytes and macrophages are the major sources of interleukin-1 and tumor necrosis factor. Endothelial cells, keratinocytes, and brain astrocytes can also produce interleukin-1 (Dinarello et al., 1988).

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Role of Interleukin-1 and Tumor Necrosis Factor in Acute Phase Response:

Besides fever, a wide variety of actions characteristic of the acute phase response can be triggered jointly by interleukin-1 and tumor necrosis factor. many of these actions also involve arachidonate intermediates. These include myelopoiesis, release of neutrophils (Kampschmidt, 1981) and augmentation of neutrophil function, stimulation of lymphocytes B-cell proloferation with antibody production (Lipsky et al., 1983), T-cell activation and elaboration of interleukin-2 (Mizel, 1982).

Induction of acute phase synthesis and secretion by hepatocytes (Pepys and Baltz, 1983), increased production of ACTH, beta-endorphins, growth hormone and vasopressin from the pituitary (Neufeld et al., 1980), induction of fibroblast proliferation, osteoclast activation and release of collagenase from chondrocytes, induction of slow-wave sleep activity in the brain (Dinarello, 1984). Tumor necrosis factor and to lesser extent, interleukin-1 may contribute to the wasting characteristic of chronic infections and other inflammatory or neoplastic disease by these mechanisms as well as by inhibition of appetite. In all of these actions as well as in the production of fever interleukin-1 and tumor necrosis factor-alpha can act synergistically or additively (Dinarello et al., 1988).

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SYNTHESIS AND SEGREGATION OF SECRETORY PROTEINS BY THE LIVER

The liver synthesize the acute phase proteins in response to interleukin-1, tumor necrosis factor-alpha, interleukin-6, hepatocyte-stimulating factor III as well as corticosteroids (Baumann and Gauldie, 1990).

As a general rule, mRNA's coding for intracellular cytoplasmic proteins and for nuclear encoded mitochondrial proteins are translated by cytoplasmic ribosomes, where as in mRNA's coding for proteins destined for secretion are translated by ribosomes on the surface of the endoplasmic reticulum (Schatz, 1979).

Signal Hypothesis:

Each protein undergoing assembly has specific properties that determine its own intracellular site of synthesis as well as its post-translation fate. It has been shown that the amino acid composition and secondary structure of the NH_2-terminal portion of the nacent polypeptide provides a mean by which specific intracellular factor can identify the protein as one destined for secretion (Blobel and Dobberstein, 1975).

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During translation, the signal sequence is removed proteolytically from the polypeptide in a reaction catalyzed by an intraluminal endopeptidase known as the signal peptidase (Jackson and Blobel, 1979 and Walter et al., 1979).

Although the signal peptide plays a role in the insertion of each presecretory protein into the endoplasmic reticulum lumen, it also serves to correctly place the ribosomes on the cytosolic face of the endoplasmic reticulum membrane. There is a specific protein complex known as the signal recognition particle (SRP) which can associate reversibly with endoplasmic reticulum membrane and mediate the attachment of ribosomes containing nascent secretory proteins to the membranes of the endoplasmic reticulum (Walter and Blobel, 1981).

Translation of mRNA's for secretory proteins begins on cytoplasmic ribosomes. After a sufficient amount of nascent signal sequence emerges from the ribosomes that bears the presecretory protein, the signal peptide is recognized by the signal recognition domain of SRP which binds the ribosome in signal sequence complex. This process allows the elongation arrest domain of the SRP to temporarily halt any further polypeptide elongation (Meyer et al., 1982).

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Binding of the ribosome to the endoplasmic reticulum membrane is also facilitated by direct interaction with integral ribosome receptor proteins known as the ribophorins (Tavill, 1985).

The enzymatic removal of a signal peptide during its cotranslational insertion into the endoplasmic reticulum lumen appears to be necessary for release of the secretory proteins into the membrane as well as for its continuation along the secretory pathway.

Translation of secretory proteins across the endoplasmic reticulum, its molecular details of it is not well known, but appears that transport of polypeptide across the membrane of endoplasmic reticulum is an energy consuming process that requires hydrolysis of nucleotide triphosphatases other than those involving the polypeptide elongation (Walter and Lingappa, 1986).

Post-translational Modifications:

Proteins destined for secretion undergo numerous modifications prior to export from the cell. A newly formed polypeptides can undergo further proteolysis, glycosylation and lignad binding as well as other modifications (Vy and Wold, 1977).

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Intracellular Movement of Secretory Proteins and The Final Step of Secretion:

Once the polypeptide protein of the secretory has been completed in the endoplasmic reticulum, the protein passes sequentially from the endoplasmic reticulum to the Golgi apparatus, at this point it undergoes final processing and is packaged into secretory vesicles for export from cell by a process of exocytosis (Rothman and Lodish, 1975 and Tavill, 1985).

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ACUTE PHASE PROTEINS

The proteins of the acute phase response represents a vast and heterogenous group of plasma proteins which undergo marked change in their serum levels during most acute and chronic inflammatory processes. They are mainly synthesized by the liver cells, triggered by cytokines, mainly interleukin-1, and other cytokines as tumor necrosis factor-alpha, interleukin-6, hepatocyte-stimulating factor, as well as corticosteroids (Baumann and Gauldie, 1990).

This group of proteins is composed of alpha$_1$-antitrypsin, ceruloplasmin, haptoglobin, alpha$_2$-macroglobulin (all will be discussed in details later on), C-reactive protein, alpha$_1$-acid glycoprotein and fibrinogen.

C-Reactive Protein:

The molecular weight of C-reactive protein is 105,000, consisting of five identical non-glycosylated polypeptide subunits, which are non-covalently associated in a disk-like configuration, that has a cyclic pentameric symmetry. Each subunit consists of a single polypeptide chain of 187 amino acid residues, with a molecular weight of 21,500 (Olivera et al., 1979).

Although no definite function has been ascribed to this protein, a number of properties have been investigated. C-

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