REVIEW OF LITERATURE
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SERUM PROTEINS AND THEIR CHANGES

Some of the most important functions of the liver are connected with protein metabolism, such as deamination of amino-acids and the maintenance of normal blood levels of albumin, globulin and fibrinogen. The liver also plays an important role in the synthesis of special proteins such as those required for blood clotting. The protein synthesis is much more rapid in the liver than in any other tissues. For example, in man half life of liver proteins is 2.5 to 10 days, as compared with muscles which is 150 days (Miller & Bale, 1954).

Miller (1954) has shown that infusion of labelled amino acids into isolated perfused dog liver resulted into synthesis of plasma proteins. Similarly the experiments with isolated perfused rat liver and with heptatectomized rat demonstrated that the hepatic parenchymal cells synthesize various protein fractions like albumin, lipoproteins, glycoproteins, ceruloplasmin haptoglobin and prothrombin (Martin & Neuberger, 1957; Gordon & Humphrey 1960).

The liver also plays an important role in the catabolism of serum proteins. Gordon & Coehn and their
associates (1960) have shown that rat liver is responsible for catabolism of 13% albumin, 30% of serum globulin and also serum transferrin.

In the light of major contribution of liver in synthesis and catabolism of proteins, it is not surprising that profound alterations in electrophoretic pattern of serum proteins are observed in liver diseases. Normal person makes about 10.0 g of albumin daily. Hypoalbuminaemic patients with cirrhosis can synthesise only about 4.0 g albumin, 2.0 g of fibrinogen and 1 g transferrin daily (Sherlock, 1972; Roseoer, 1963).

A rise and fall of plasma proteins concentration may reflect changes not only in hepatic production but also in plasma volume. Total exchangeable protein (Albumin pool) is not depleted in cirrhosis. When ascites is present however, the extra vascular albumin pool is expanded at the expense of the intra vascular one (Wilkinson & Mendenhall, 1963). However, changes are slow to develop and do not immediately reflect acute liver damage. Even complete cessation of albumin production results in only 25% decrease in serum levels after eight days. In patients with continuing cholestasis serum albumin falls. The characteristic change in chronic
liver disease is a fall in serum albumin and rise in serum globulin levels.

In severe prolonged viral hepatitis and in cirrhosis serum albumin level bears a close relationship to the clinical stage and are helpful prognostically and in following treatment. Hyperglobulinaemia is a feature of chronic hepatocellular disease. It reflects a reticuloendothelial reaction to antigens. Extremely high values may characterize chronic active hepatitis and levels falling only with steroid therapy in latter stages of diseases (Sherlock, 1975).

The total plasma proteins average just over 7.0 g% with a range from 6.3 to 7.9 g%. The value for the main constituents of different fractions of serum proteins are given a little different by different workers, but may be taken to be approximately 3.7 to 5.3 g% for albumin, 1.6 to 3.6 g% for globulin and 200 to 400 mg% for fibrinogen, thus giving a albumin and globulin ratio 2.5 :1 to 2 :1 (Varley, 1980). The above data are obtained by salting out technique. The normal values of different electrophoretic fractions of serum proteins may vary from one laboratory to another depending upon the technique used. However, commonly accepted values for different electrophoretic fractions
of serum proteins as reported by King & Wooton (1956) are as follows:

- Total serum proteins  - 6 to 8 g/100 ml
- Serum Albumin         - 3.6 to 5.0 g/100 ml (55-65%)
- Serum Alpha globulins - 0.5 to 1.2 g/100 ml (4-14%)
- Serum Beta globulin   - 0.46 to 1.2 g/100 ml (7-15%)
- Serum Gamma globulin  - 0.9 to 1.9 g/100 ml (6-16%)

Martin (1960); Havens & Williams (1948) and Ricketts & Sterling (1949) reported that the concentration of total serum proteins was not significantly reduced in acute viral hepatitis, but beta globulin may be increased and gamma globulin was found to be within normal limits. Diminished concentration of Alpha globulins has been co-related with the severity of the viral hepatitis (Dommelen et al, 1959). These changes occur early in the course of disease and may be detected before the appearance of jaundice and usually disappear with in 8 to 12 weeks (Havens, 1962; Krugmen and Wander, 1962).

Progressive increase in the concentration of gammaglobulin during follow up after the onset of viral hepatitis may be observed in patients who are undergoing a transition from acute to chronic hepatitis (Ossarmen and Takatsuki, 1963). Similarly a marked decrease in
serum albumin and an increase in gamma globulin may as such reflect to a large extent the level of circulating antibody (King & Wooton, 1956)

Chronic persistent hepatitis is a benign disease. Serum globulin levels may be slightly elevated during the first year of disease but return to normal thereafter (Docher et al., 1970). In patients of chronic active hepatitis marked decrease in total albumin and a greatly increased gamma globulin concentration has been reported by Galsayd & Krisnor (1967) and Mistillis and Blackburn (1970).

In portal cirrhosis there was a significant decrease in the mean concentration of total serum proteins, serum albumin and alpha globulins, whereas the concentration of beta and gamma globulin was increased markedly (Gray & Barron, 1943; Sundarman et al., 1963). In these patients a profound decrease in serum albumin concentration is attended by a poor prognosis (Post and Patak, 1942). A characteristic feature of the electrophoretic pattern in hepatic cirrhosis is the phenomenon of beta-gamma bridging which means a lack of demarcation between the peaks of beta and gamma globulin (Demeulenare and Weime, 1961). The increase in the level of globulin is mostly due to increase synthesis by reticulo-endothelial

In post necrotic cirrhosis the concentration of gamma globulin is usually greater than in Laennec's cirrhosis and the degree of hypergammaglobulinaemia may be a valuable laboratory aid in the differentiation of these forms of cirrhosis (Gross et al., 1959; Wolff et al., 1958 and Paronetto et al., 1962).

In cryptogenic cirrhosis the serum gamma globulin may rise five to seven times above normal. The hypergammaglobulinaemia of this magnitude is ordinarily not seen in cirrhosis of alcoholics and its presence is therefore of diagnostic value (Bjornboe and Reaschon, 1949 & Zimmerman, 1961).

In primary biliary cirrhosis the hyperbeta-globulinaemia with hypoalbuminaemia was reported by Ahrens and Coworkers, 1949 and Sterling & Ricketts, 1949). In Cholestasis the serum albumin is usually normal until the terminal cell failure. When serum albumin falls and globulin increases (Sunderman et al., 1968).

In metastatic carcinoma of liver the mean concentration of total serum proteins was found to be reduced significantly. The concentration of alpha-1 globulin was increased and those of beta and gamma globulins were normal (Sunderman and Jared, 1969). The Alpha-1
globulin contains glycoproteins and is low in hepatocellular diseases, falling in parallel with the serum albumin. An increase accompanies acute febrile illness and malignant disease (Russ et al., 1956). In primary carcinoma of liver in addition to raised alpha-1 globulin, a rise of alpha-2 globulin may also be encountered (Viallet et al., 1962).

**SERUM IMMUNOGLOBULINS**

The gamma globulins were first recognised and designated as a distinct group of serum proteins by Tiselius (1937). Tiselius and Kabot demonstrated that the antibodies of serum are present in the gamma globulins. An additional knowledge accumulated, the gamma globulin of serum was found to be composed of at least five distinct globulins with antibody activity separable by antigenic analysis (Committee on nomenclature of human immunoglobulin W.H.O. Bull, 1964).

The four classes of immunoglobulins have been identified known as IgG, (Yg, 7S, Y2 globulin), IgA (Ya, B2-A globulin), IgM (YM, 19S, Y macroglobulin) and IgD (YD). The immunoglobulins also include other myeloma proteins which are structurally related to antibodies like myeloma proteins and Bence Jones proteins (Fahey, 1965). Recent work on P-K antibody (reagin) indicates that it belongs to a distinct immunoglobulin class.
designated as IgE. It is present in very small amount in serum and has a sedimentation rate approximately 85 (Russell & Weiser, 1971).

The IgM molecules are largely intravascular in location (80% in contrast to 40% for IgG) and are catabolized more rapidly (14% of body pool per day in contrast to 3% per day for IgG). These features of IgM antibody are useful characteristics, if antibody is only needed for short time and where continued production of this size is disadvantageous. Recent evidence indicates that IgM antibody synthesis actually shuts off, when IgG antibody synthesis starts (Fahey, 1965). IgG constitutes the largest part about (75%) of the total immunoglobulins concentrations with a serum level of 1.2 g/100 ml. The serum level of IgM is about 0.12 g/100 ml i.e. about 7% of total immunoglobulins. The serum level of IgA is about 0.39 g/100 ml i.e. 21% of total immunoglobulins (Fahey, 1965 b).

Row and Fahey (1965 a+b) described a new immunoglobulin and labelled it as IgD. The serum level of IgD varies very widely but median level of 0.003 g/100 ml has been accepted.

Hepatic diseases differed in their pattern of
immunoglobulin disorders as suggested by Fahey (1950). Patients with Laennec's cirrhosis typically had markedly increased IgG and IgA but normal IgM levels. The patients with biliary cirrhosis have shown elevated level of IgM with normal IgG and IgA level. In patients with viral hepatitis Hermans found that all immunoglobulins were increased. In hepatoma IgM tended to be reduced.

Lo Grippo and associates (1966 b) have studied 60 mentally retarded children of viral hepatitis aged 1-15 years in different stages of disease. They noticed a normal level of IgG, IgM and IgA in icteric phase of the disease. In group-2 i.e. after one month of disease IgM values were increased above normal. After 4 months of disease the values of both IgG and IgM were above normal. The values of IgG only was found to be elevated after 6 months of disease. The IgM level came down to normal. The level of IgA remained unchanged. This study suggested that primary response to infectious hepatitis is an elevation of IgM and followed by elevated level of IgG, while IgA level was within normal limits.

Gleichmann and Bicher (1963) also reported similar observations, but in contrast to the Lo Grippo's findings they noted a very little increase in IgG levels in hepatitis sera. They suggested that increase in IgG
level might be a sign of chronic active hepatitis. In patients with chronic active hepatitis the typical immunoglobulin pattern is of very high IgG globulin level with a notable increase in IgM and IgA level (Lee, 1965). This should be compatible with an immunological response to continuing antigenic stimulus. Similar findings were also reported by Deicher et al (1969); Feizi and Maclachlan et al (1965). In crypo-
genic cirrhosis the level of IgG, IgA and IgM all were increased as reported by Deicher et al (1969), Feizi (1969) and Maclachlan (1965). The value of IgG were not that pronounced as in chronic active hepatitis.

In patients with alcoholic cirrhosis the IgA level was markedly elevated but this is not certainly specific for alcoholic cirrhosis (Lee, 1965; Deicher et al., 1969 and Feisi, 1968).

The raised levels of IgM were reported in primary biliary cirrhosis by Feisi (1961) and Paronetto, F. (1964). This rise is usually not found in drug cholestatis or in extra hepatic biliary obstruction and may therefore be helpful in differential diagnosis of these diseases (Nobbe, 1966 and Sherlock, 1970). Paronetto and Popper reported that in primarily biliary cirrhosis the IgM was present in large basophillic cells aggregation of complemet and antibody complex around the bile ducts.
ASCITIC FLUID IN CIRRHOSIS OF LIVER

The development of ascites is the commonest major complication of cirrhosis liver and implied a poor prognosis (Ratnoff and Patek, 1942; Sherlock, 1953). The ascitic fluid has the characteristic of an ultrafiltrate of plasma augmented by varied amount of plasma proteins and thus represents an expansion of extra cellular space. The constituents are in dynamic state of equilibrium with the remainder of the body fluids (Schoenberger et al, 1952).

Specific immunoelectrophoresis and immunoprecipitin techniques have amply confirmed the presence in the ascitic fluid and other extravascular fluid spaces nearly all the different plasma proteins (Aabo et al, 1963). The transport of albumin into ascitic fluid has long been a source of interest for the accumulation and disappearance of this fluid may occur rapidly and not always in relationship to understandable disease processes. Zilman and co-workers (1969) using isotopic procedures have suggested that all the albumin moving into ascitic fluid in patients of cirrhosis could not have been derived from the systemic circulation. A more direct extra vascular route either by direct
lymphatic drainage or by direct loss through the hepatic capsule might be involved. Analysis of ascitic fluid and its paper electrophoresis may help in clinical diagnosis. A strong qualitative resemblance in protein patterns between ascitic fluid and plasma with a tendency for the albumin and alpha-1 globulin fractions to be present in higher concentrations and for the alpha-2, beta and gamma globulins to be present in slightly lower concentrations in ascitic fluid than the plasma has been reported (Schulzke and Hermans, 1966).

Almost all the immunoglobulins (IgG, IgM and IgA) were reported in ascitic fluid (Szabo et al, 1963). Chodirker and Tomasi (1963) reported that IgA is the predominant immunoglobulin in sero mucus secretions. Such secretory IgA is found only in external secretions like saliva and tracheobronchial secretions while internal secretions like pleural fluid, ascitic fluid, synovial fluid, amniotic fluid and cerebrospinal fluid, IgA is not of secretory type. The IgG and IgA ratio is similar to plasma that is approximately 5:1 in internal secretions.