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Scientific Basis of Clinical Practice

Ascites and Oedema in Liver Disease

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British Medical Journal, 1973, **3**, 336-338

The mechanism of the formation of ascites and oedema in chronic liver disease is complex: in addition to redistribution of fluid there is an overall increase in the water content of the body. Though the two processes inter-relate, it is convenient to consider separately changes in the local equilibrium between the plasma and the extracellular spaces, resulting in the redistribution of fluid, and effects on renal function, resulting in overall salt and water retention by the body.

Local Equilibrium between the Plasma and the Extracellular Fluid

In the last analysis the accumulation of extracellular fluid in the tissues to form oedema and the accumulation of extracellular fluid in the peritoneal cavity to form ascites must represent a disturbance of the local equilibrium between the formation of extracellular fluid and its removal.

THE STARLING EQUILIBRIUM

In 1896 Starling¹ propounded the view that the interchange of fluid between capillaries and tissue spaces depends on the resultant of the hydrostatic and osmotic forces inside and outside the vessel. Similarly these forces acting between the extracellular fluid spaces and the peritoneal cavity determine the transfer of fluid to form ascites. Thus the resultant of the hydrostatic and osmotic gradients between the capillaries and the peritoneal cavity determine the formation or reabsorption of ascites.

There are two known physiological factors which may favour the formation of fluid within the peritoneal cavity in patients with liver disease. Firstly, hypoalbuminaemia, which is due partly to decreased synthesis of albumin by the liver and partly to an increase in the plasma volume. The low plasma albumin concentration tends to reduce the colloid osmotic force retaining fluid within the circulation, allowing leakage of fluid into the extracellular spaces as oedema and sequentially the transfer of extracellular fluid into the perito-

neal cavity to form ascites. The second factor is portal, and hepatic sinusoidal, hypertension. In chronic liver disease accumulation of fluid within the peritoneal cavity is favoured by increased intravascular pressures—firstly, in the portal venous system and hence in the splanchnic capillaries, and, secondly, in the hepatic sinusoids.

Thus there are two possible sources of ascitic fluid; the fluid may weep through the surface of the liver as a result of increased sinusoidal pressure² or may weep through the serosal surface of the intestine as a result of increased splanchnic capillary pressure.³ Fluid weeping through the surface of the liver is a sinusoidal filtrate which, because of the great permeability of the endothelial wall, has a relatively high protein concentration approximating that of plasma, as has hepatic lymph.⁴ This accounts for the relatively low protein content of ascitic fluid in patients with cirrhosis of the liver,⁵ and together with other ancillary evidence⁶ suggests that the serosal surface of the intestine is a major source of ascitic fluid in this condition.

LYMPHATIC DRAINAGE OF PERITONEUM

Counteracting the tendency to formation of ascitic fluid is the removal of fluid by the lymphatic system. Only after exhaustion of the capacity of the lymphatic system to remove fluid does ascites accumulate.⁷ An increased flow of thoracic duct lymph occurs in cirrhosis—even without ascites⁴—suggesting that increased transudation of fluid into the extracellular spaces can initially be compensated without the formation of ascites. Dilution of lymph by the carriage of excess transuded fluid presumably contributes to the observed lowering of the protein content of the lymph in patients with cirrhosis.⁸

Possibly a relative constriction at the outflow of the thoracic duct into the venous system⁹ may be a critical factor in the formation of ascites. If this were the case then cannulation of the thoracic duct, allowing easy loss of fluid from the lymphatic circulation, would cause regression of ascites. Nevertheless, recent studies have not confirmed this.¹⁰

DYNAMICS OF ASCITIC FLUID FORMATION

Ascitic fluid is not a static reservoir. Studies using radioactive water and protein show that there is a rapid flux of both substances into and out of ascitic fluid.¹¹ Nevertheless, the maximum rate of net reabsorption of ascitic fluid in the presence of portal hypertension is strictly limited and is

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much less than the maximum rate of reabsorption of oedema fluid or the rate at which fluid can be lost from the body by diuresis.¹² In contrast, the rate of formation of ascites may be extremely rapid in such patients, particularly if there is a reservoir of fluid in the form of oedema, emphasizing the preferential localization of retained fluid as ascites rather than oedema in such patients.¹²

In summary it appears that the transfer of fluid into the peritoneal cavity in cirrhosis of the liver depends on the local balance of hydrostatic and colloid osmotic forces, probably largely across the splanchnic bed but also to some extent across the hepatic sinusoidal bed. The presence or absence of ascites depends on the balance between the resultant of hydrostatic and osmotic forces and the absorptive capacity of the lymphatic system. In contrast to the accumulation of fluid in other diseases associated with a lowered plasma albumin concentration, ascites in liver disease tends to occur more readily than oedema since there is the local factor of venous hypertension to add to the general factor of a lowered plasma colloid osmotic pressure.

Altered Renal Function

Owing to a combination of many inter-related factors (fig.) renal function is altered in patients with chronic liver disease and leads to salt and water retention.

Suggested mechanisms of sodium retention in cirrhosis. (G.F.R. = glomerular filtration rate)

REDUCED BLOOD FLOW

Reduced total renal blood flow—as measured by techniques such as PAH clearance, nitrous oxide, and ¹³³Xe washout—is a common finding in cirrhosis, especially in the presence of ascites.¹³⁻¹⁵ The reduced renal perfusion is not due to diminished cardiac output.¹⁶ Cardiac output is usually normal in cirrhosis but may be raised^{13 16-18} as a result of peripheral vasodilatation.^{17 18} Nevertheless, the cardiac output may still be suboptimal for renal perfusion since, though plasma volume may be raised in patients with cirrhosis,¹⁹ further expansion of plasma volume causes a further increase in cardiac output and also results in an increase in renal blood flow.²⁰ In patients with cirrhosis the capacity of the circula-

tion is probably increased but a major portion of the plasma volume is contained within the expanded portal and splanchnic venous beds and collateral veins. This consideration has led to the concept of a reduced “non-portal” or “effective” plasma volume being responsible for changes in renal function resulting in sodium retention.²¹ Lieberman *et al.*,²² however, found no rise in plasma volume during spontaneous diuresis, and took this as evidence against a diminished “effective” plasma volume.

Renal vasoconstriction must be considered as a possible cause of reduced renal blood flow, and indeed there is good evidence for this.^{13 23} The cause of this vasoconstriction is not known but it may be related to circulating vasoactive substances.

INTRARENAL ARTERIAL SHUNTING

The blood flow within the kidney is redistributed in cirrhosis,^{15 23} resulting in reduced flow to the outer cortex, where the main mass of functioning glomeruli is situated, and increased flow to juxtamedullary nephrons, which have a greater capacity for sodium reabsorption since they have longer loops of Henle.²⁴ This redistribution therefore reduces the glomerular filtration rate and increases sodium reabsorption. The mechanism of redistribution of renal blood flow is not known, but Kew *et al.*¹⁵ suggest renal cortical vasoconstriction due either to increased sympathetic tone or to a circulating vasoactive substance released from, or not metabolized by, the cirrhotic liver. Similar effects have been described in other liver diseases, and in portal hypertension of extrahepatic origin, even without obvious fluid retention.^{25 26}

GLOMERULAR FILTRATION RATE (G.F.R.)

In patients with cirrhosis there is commonly a reduction in G.F.R. at least partly due to the reduced renal blood flow and the intrarenal arterial shunting discussed above. Baldus¹³ found that patients with resistant ascites had significantly lower glomerular filtration rates than those with ascites which responded readily to diuretics, while nearly all patients without ascites had normal filtration rates.

The effects of a reduced G.F.R. are: (1) limitation of the quantity of solute available for excretion, and (2) reduction of tubular fluid flow and consequent increased opportunity for proximal tubular reabsorption of sodium—and hence of water. Nevertheless, a change in G.F.R. is not thought to be an important factor in the control of sodium excretion.²⁷

INCREASED REABSORPTION OF SODIUM

In cirrhosis the predominant excessive reabsorption of sodium is in the proximal tubule (and the proximal part of the distal tubule which is functionally part of the proximal tubule), as can be inferred by studying the effects of thiazides and aldosterone antagonists on sodium excretion.²⁸ Increased proximal tubular reabsorption of sodium may be partly due to the diminished glomerular filtration rate, but this is unlikely to explain the extremely avid reabsorption seen in the presence of ascites. The cause of this avid proximal reabsorption of sodium is not known but may be due to a decrease in activity of the “third factor.” This is a postulated natriuretic hormone, which seems to control proximal tubular reabsorption of sodium in response to alterations of the plasma volume.^{27 29} The reduced “effective” plasma volume in patients with cirrhosis may result in diminished activity of the hormone and consequent increased sodium reabsorption.

The hormone aldosterone causes sodium reabsorption by the distal tubules. Changes which can result in an increased

aldosterone level are decreased afferent arteriolar blood flow to the glomeruli³⁰ and alterations in composition of the fluid contained in the distal convoluted tubule.³¹ It is thought that a rise in aldosterone release is brought about by the juxtaglomerular apparatus responding—to diminished blood pressure in the afferent arteriole and to stimuli from the macula densa of the distal tubule—by increasing its renin secretion. Renin causes the formation of angiotensin I and then angiotensin II from a circulating precursor, the angiotensin II then causing the release of aldosterone and possibly also acting directly on the tubules to cause sodium retention. Aldosterone probably acts largely in the fine adjustment of sodium excretion, major changes in sodium excretion being mediated at the proximal convoluted tubule.

In patients with cirrhosis and ascites the number of granules in the juxtaglomerular apparatus is increased,^{32, 33} there is an increase in height of the macula densa³² and in the width of the zona glomerulosa of the adrenal cortex,³³ and increased amounts of aldosterone are present in the urine,³⁴ all suggesting increased aldosterone production. In addition to increased production of aldosterone there may be diminished inactivation of aldosterone by the cirrhotic liver.³⁵ There is some evidence that the effects of angiotensin on the renal tubule may differ in the patient with cirrhosis and ascites from those in normal people.³⁶ In addition, arterial hypertension is rarely observed in patients with cirrhosis of the liver despite increased activity of the renin-angiotensin-aldosterone system, suggesting a lack of peripheral response to angiotensin.³³

Increased distal tubular reabsorption of sodium under the control of aldosterone occurs only if proximal tubular reabsorption is not complete, and is at the expense of increased potassium excretion. Thus the use of frusemide or thiazides (which allow more sodium to reach the distal tubule) will increase the loss of potassium in the urine. Spironolactone, which antagonizes the effect of aldosterone on the distal tubule, can obviously have no effect if proximal sodium reabsorption is complete but augments the action of frusemide and thiazides and reduces the potassium loss associated with these diuretics.

In summary there are changes in the blood flow to the kidney and in the functioning of the glomeruli and tubules which combine to result in bodily retention of salt and water and thus provide a source of the fluid which accumulates, as ascites and oedema, in response to changes in the local equilibrium between plasma and extracellular fluid.

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