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Disturbances in Lipid Metabolism Associated with Chylothorax and its Management

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Changes in circulating lipid status were studied in a 70-year-old woman during management of chylothorax that included chest drainage, pleuroperitoneal shunting, and a successful thoracic duct ligation. Hypolipidemia with a relative decline in high-density lipoprotein (HDL) cholesterol was apparent at presentation. Following recovery, serum HDL cholesterol rose to the upper limit of normal. Apolipoprotein A-I (Apo A-I) was discordantly raised during the period of pleuroperitoneal shunting. We speculate that diversion of chylomicrons to the liver with subsequent hydrolysis accounted for a release of Apo A-I particles into the circulation at a time when the formation of HDL was compromised by a state of starvation. (Henry Ford Hosp Med J 1991;39:49-51)

Chylothorax, a collection of chyle in the pleural space due to leakage from the thoracic duct, is an uncommon disorder. It occurs at all ages as a manifestation of congenital, inflammatory, and neoplastic diseases (1). Diagnosis is usually easy: pleural fluid is milky-white and has a high triglyceride concentration, and lipid stain is positive and contains a preponderance of lymphocytes (1). Management is difficult, and the disorder is accompanied by considerable morbidity and mortality. Conservative management of low-fat diet, intravenous feeding, and continuous chest drainage is frequently unsuccessful. Surgical management, such as thoracic duct ligation (1) or the more recently described procedure of pleuroperitoneal shunting (2), has a more favorable outcome. The effect of chylothorax on lipid metabolism has not been reported previously. We followed the lipid changes in a patient with spontaneous chylothorax throughout the course of her illness and management. The findings are reported and the wider implications of these lipid changes with respect to fat metabolism are discussed.

Case Report and Methods

A 70-year-old woman presented with a two-month history of progressive dyspnea. She had a history of pneumonia and smoked 25 cigarette packs/year. A chest radiograph two years prior to presentation was normal. On examination she weighed 49 kg (107 lb) and was 159 cm (63.6 in) tall. The right lung base was dull to percussion with diminished breath sounds and vocal resonance. There were no signs of right heart failure. Chest radiograph demonstrated an extensive right pleural effusion. A thoracentesis yielded over a liter of white fluid. Analysis of fluid gave the following results: protein 5 g/L (<0.5 g/dL), glucose 12.2 mmol/L (220 mg/dL), lactate dehydrogenase 0.83 μ kat/L (50 U/L), WBC count 2.6×10^9 /L (2,600/ μ L) with 96% lymphocytes, cholesterol 2.62 mmol/L, and triglyceride 61.8 mmol/L. Routine and mycobacterium cultures were negative. Complete blood count and electrolyte profile were within normal limits. Both SGOT (73 IU/L) and SGPT (59 IU/L) were mildly elevated. Serum total protein was 54 g/L (5.4 g/dL) and serum albumin was 34 g/L (3.4 g/dL). A chest drain was in-

serted. The patient was placed on a diet rich in medium chain triglycerides. Chylous drainage continued in excess of one liter daily. Two weeks after admission, a Denver shunt was inserted for unidirectional flow from the right pleural space to the peritoneal cavity. The pumping chamber was placed over the lower ribs in a subcutaneous tunnel and the patient was instructed in its use before being discharged home. One month later she was readmitted because of persistent ascites, bilateral pleural effusions, and progressive abdominal pain. A right thoracotomy was performed, the shunt removed, and the thoracic duct ligated. No obvious predisposing lesion was identified. She had an uneventful recovery with resolution of pleural effusions and ascites.

Blood samples were drawn after an overnight fast for determination of serum total cholesterol, triglycerides, albumin, high-density lipoprotein cholesterol (HDL-C), apolipoprotein A-1 (Apo A-1) and apolipoprotein B (Apo B). Total cholesterol and triglyceride were measured with a SMAC II (Technician Instrument Corp, Tarrytown, NY) using the methods of Allain et al (3) and Bucolo and David (4), respectively. HDL-C was measured by the Kostner method (5). Serum low-density lipoprotein cholesterol (LDL-C) was calculated according to the formula of Friedewald et al (6). Apo A-1 and Apo B were measured by a nephelometric method with Alert™ apolipoprotein kits (Travenol Laboratories, Inc, Deerfield, IL) giving respective reference ranges of 94 to 174 mg/dL and 46 to 120 mg/dL. Eight sets of measurements were obtained: one just before insertion of the shunt, three while the shunt was in situ, and four after ligation. Informed consent was obtained from the patient.

Two years prior to presentation, fasting serum cholesterol was 5.25 mmol/L and serum triglyceride was 0.79 mmol/L. At presentation they were 3.67 mmol/L and 0.51 mmol/L, respectively. Following a diet

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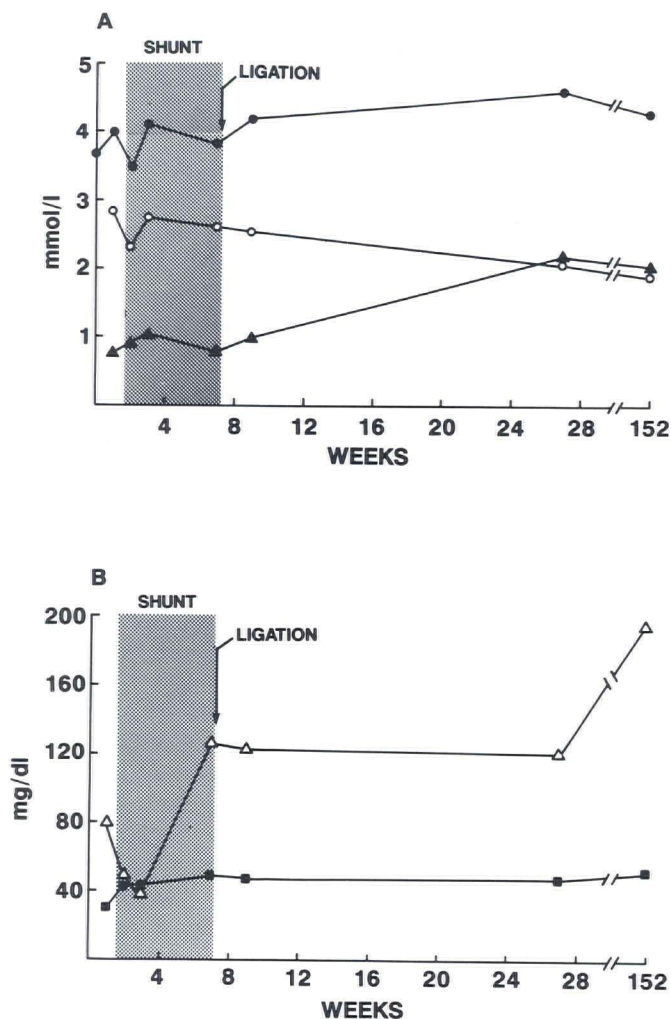
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Figure—Plot of serum total cholesterol (closed circle), LDL-C (open circle), HDL-C (closed triangle) in panel A and of Apo A-1 (open triangle) and Apo B (closed square) in panel B. Values at 27 weeks represent the average of two sets of results. The reference ranges are: total cholesterol = < 5.12 mmol/L, HDL-C = > 0.63 mmol/L, LDL-C = < 1.49 mmol/L, Apo A-1 = 94-174 mg/dL, and Apo B = 46-120 mg/dL.

rich in medium chain triglycerides, serum cholesterol was 4.0 mmol/L and serum triglyceride was 0.89 mmol/L. At that time, serum HDL-C was low at 0.75 mmol/L and the calculated LDL-C was 2.84 mmol/L. Serum Apo A-1 (79 mg/dL) and serum Apo B (< 40 mg/dL) were low. Serum total cholesterol remained low following insertion of the shunt but rose to 4.63 mmol/L after ligation of the thoracic duct (Figure). Serum triglyceride remained unchanged by these procedures. Serum HDL-C rose slightly after the shunt and markedly after the ligation. LDL-C fell after each procedure and the final value was low at 1.89 mmol/L. Serum Apo A-1 rose to 126 mg/dL just prior to removal of the shunt and remained the same immediately after surgery; the final value nearly three years after ligation was high at 188 mg/dL (Figure). Serum Apo B levels rose steadily from an undetectable level and remained within the low-normal range. Serum albumin had fallen to 26 g/L (2.6 mg/dL) pre shunt, was 33 g/L (3.3 mg/dL) during shunting, 26 g/L (2.6

mg/dL) immediately post shunting, and 44 g/L (4.4 mg/dL) four months post ligation.

Discussion

A persistent leakage of chyle from the thoracic duct leads to inanition quite rapidly. Spontaneous closure of the defect is facilitated by a diet rich in medium chain triglycerides as this causes a reduction in the chyle flow. Such dietary intervention alone is generally sufficient to alleviate the symptoms of chylothorax (1,2). Drainage of the chest cavity, as a temporary measure to relieve respiratory distress, also permits closure to occur, but loss of essential nutrients enhances the malnourished state. A novel surgical solution recently proposed involves shunting chyle into the abdominal cavity from the chest (2). Ligation of the thoracic duct is the curative procedure when all else fails; chyle then reaches the systemic circulation via lymphatic collaterals (1).

Our patient had no known history of lipid disturbance based on normal cholesterol and triglyceride levels recorded in the past. Indeed, based on the final set of values obtained nearly three years following recovery, the patient had a high-normal HDL-C and a low LDL-C. No cause was identified for the development of chylothorax despite extensive studies and a surgical exploration. Minor trauma, such as back flexion, likely led to rupture of the duct. Apart from the rare association of hypobetalipoproteinemia with lymphangiectasia resulting in chylous effusions (only reported in one member of an afflicted family) (7), there is no known relation between primary lipid disorders and chylous leakage. It seems reasonable to assume that any alterations in lipid metabolism in this patient were manifestations of chylothorax and its treatment.

The four classes of lipoprotein molecules—chylomicrons, very low density lipoprotein (VLDL), LDL, and HDL—are necessary for the transport of energy-rich but insoluble triglycerides from both the intestine and the liver to peripheral sites where they are stored or used (8). Thus, the lipoproteins all share a similar structure of a hydrophilic surface with a hydrophobic core. There are close and, as yet, inadequately understood interactions between the various lipoproteins (8). Lipoproteins either originate at the sources of triglycerides synthesis (chylomicrons from the intestine, and VLDL from the liver) or can be generated in the circulation as is the case for LDL and HDL. Nascent HDL particles that are synthesized in the liver have a disc shape; transformation into a spherically-shaped functional particle occurs in the circulation by lecithin cholesterol acyl transferase. Apo A-1, the main surface protein moiety of HDL, is synthesized in the intestine and liver, and its measurement is now considered to reflect HDL concentration in serum, whereas measurement of Apo B is considered to indicate LDL concentration, since its major surface protein is Apo B100. In our case, discordancies were noted between the concentrations of the Apo A-1 and HDL-C and between Apo B and LDL-C.

The lipid levels observed at presentation and prior to insertion of the shunt likely reflected the patient's poor nutritional status. Serum total cholesterol and triglyceride were well below baseline values recorded two years previously when the patient was in good health. All other lipid measurements were low. The

HDL-C was relatively lower than the LDL-C at this stage, a finding that has been reported as a feature of starvation in humans (9). Following insertion of the pleuroperitoneal shunt (when there was no change in the patient's nutritional status), serum total cholesterol and triglyceride did not alter. Modest increases were observed in HDL-C and Apo B; consonant with a steep rise in Apo A-1. After recovery from thoracic duct ligation and return of good health, the patient's serum total cholesterol and triglyceride had risen closer to baseline. This was accompanied by a substantial rise in HDL-C and a further fall in LDL-C. Apo B remained low and Apo A-1 rose ultimately to above the upper limit of normal.

Apart from the steep rise in Apo A-1, all changes in lipid levels after insertion of the shunt probably could be attributed to malnutrition. We postulate that the discordance between HDL-C and Apo A-1 is explained by the combined effect of two contemporaneous events: diminished hepatic protein synthesis during the malnourished state, and preferential catabolism of chylomicrons by hepatic triglyceride lipase. Hepatic protein synthesis is undoubtedly decreased in a malnourished state. This is reflected in our patient by the low levels of serum albumin and could account also for the consistent reduction in Apo B levels and presumably could mitigate the production of nascent HDL particles. By contrast, intestinal synthesis of Apo A-1 appears to be altered minimally by reduction in fat intake, at least in studies of rat enterocytes (10,11).

The destination of chyle that is diverted into the peritoneum is unknown, but chyle probably reaches the liver via the portal circulation (2). Chylomicrons would then be exposed to the action of hepatic triglyceride lipase (12,13). This enzyme, although less potent than its counterpart in the periphery (lipoprotein lipase), appears in animal studies to be enhanced during starvation (14). The activity of lipoprotein lipase in adipose tissue and skeletal muscle of humans is reduced by starvation (15). Hydrolysis of chylomicrons reaching the liver could lead to the release of remnants such as Apo A-1, as well as provide energy sources such as fatty acid and monoglyceride. Contemporaneously, generation of HDL should be attenuated for a number of reasons: low levels of chylomicrons in the systemic circulation due to interruption in flow from the injured thoracic duct; low levels of VLDL due to malnourished state; relative decline in lipase activity in the periphery compared to the liver as part of an energy conservation mechanism necessitated by state of starvation; and diminished hepatic output of nascent HDL particles. This combination of events by virtue of both the thoracic duct injury and the diversion of chyle to the liver through the shunt could explain the discordance between Apo A-1 and HDL-C levels. The disproportionate elevation of Apo A-1 would be sustained as long as there was deficient generation of HDL in the face of chylomicrons passing to the liver directly from the leaking thoracic duct via the Denver shunt.

In conclusion, patients with persistent chylous drainage can develop hypolipidemia as a result of malnutrition and can manifest an unfavorable balance between LDL-C and HDL-C. Diversion of chyle into the peritoneum causes a discordant increase in a surface apolipoprotein, Apo A-1, the importance of which both for the individual patient and for genesis of HDL has yet to be fully elucidated. Further study of similar patients is recommended because it provides a unique opportunity to explore various aspects of lipoprotein metabolism.

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