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LIVER DISEASE

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Summary

The liver is the largest and most complex metabolic organ of the body, with critical functions for anabolism, detoxification, and protection from gut-derived toxins; these functions are negatively affected in advanced liver disease. Malnutrition in liver disease is multifactorial, and its assessment is difficult because of the overlap of markers of liver disease with those of malnutrition. However, a subjective global assessment plus selective laboratory tests are usually adequate for identification of malnutrition. Advanced liver disease is strongly associated with malnutrition, and the severity of malnutrition correlates with the development of complications of liver disease, as well as mortality. Intense nutritional support can improve malnutrition in patients with liver disease, and may decrease infectious complications, improve cognitive function, and in some instances even decrease mortality.

Some individual nutrients used in high doses have shown beneficial effects in specific liver diseases, and others are promising. For example, vitamin E improved liver enzymes and histology in non-alcoholic steatohepatitis (NASH). Other therapeutic interventions which are considered "complementary and alternative medicine" may have some value, but need more study.

Obesity with insulin resistance is also a widespread problem and frequently leads to non-alcoholic fatty liver disease (NAFLD) and in some instances to NASH and cirrhosis. Indeed, NASH is now recognized as the major cause of cryptogenic cirrhosis. Excessive intake of some specific nutrients, such as n-6 fatty acids and fructose, has been implicated in the development of NASH. Dietary modifications with weight loss, increased physical activity, and bariatric surgery have all been shown to improve the hepatic steatosis.

In patients in need of liver transplantation, both undernutrition and obesity increase the rate of complications and length of stay after liver transplant. Correction of these problems is an important component of the pre-transplant management.

Introduction

The liver is the largest organ in the body, weighing approximately 1.5 kg in adults, and it is possibly the most complex organ in terms of metabolism. It has a unique dual blood supply, being perfused by both the portal vein and the hepatic artery, and comprises multiple cell types that have different functions. Hepatocytes make up over 80% of total liver mass and play a critical role in the metabolism of amino acids and ammonia, biochemical oxidation

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reactions, and detoxification of a variety of drugs, vitamins, and hormones. Kupffer cells represent the largest reservoir of fixed macrophages in the body. They play a protective role against gut-derived toxins that have escaped into the portal circulation, and are a major producer of cytokines, which can markedly influence nutritional status. Hepatic stellate cells are the major storehouse for vitamin A in the body, and play an important role in collagen formation during liver injury. Other specific cell types also have unique functions (e.g., bile-duct epithelium in bile flow sinusoidal endothelial cells in adhesion molecule expression and endocytosis). The liver plays a vital role in protein, carbohydrate, and fat metabolism as well as in micronutrient metabolism. It synthesizes plasma proteins, non-essential amino acids, urea (for ammonia excretion), glycogen, and critical hormones such as the anabolic molecule, insulin-like growth factor-1. The liver is a major site for fatty acid metabolism, and bile from the liver is needed for fat absorption from the intestine. Thus, it seems obvious that the liver is important for proper nutrition.

A strong association exists between advanced liver disease and malnutrition. However, malnutrition is not always recognized in patients with liver disease, at least in part because weight loss in these patients can be masked by fluid retention. The loss of glycogen stores predisposes patients with advanced liver disease to enter a starvation state within a few hours of fasting that can lead to further protein catabolism and loss of function. Therefore, it is important to recognize malnutrition and initiate nutrition support early in these patients. Moreover, obesity and the metabolic syndrome are increasingly recognized as a major cause of abnormal liver enzymes and a spectrum of non-alcoholic fatty liver disease (NAFLD). Thus, both undernutrition and obesity play important roles in liver disease.

This chapter begins with a discussion of the prevalence of malnutrition and nutritional assessment in patients with liver disease. Causes of malnutrition and cytokine-nutrient interactions are then discussed, followed by a review of nutritional support, including obesity, in liver disease, as well as nutrition and liver transplantation.

Assessment and Prevalence of Malnutrition

Malnutrition is widely present in liver disease, especially in more severe, chronic forms. When evaluating information concerning the prevalence of malnutrition in cirrhosis, it is important to use tests that accurately define nutritional status. Unfortunately, assessment of nutritional status in patients with liver disease is often quite difficult. Tests that are most frequently used include serum visceral protein concentrations, some assessment of immunity (total lymphocyte count or delayed hypersensitivity), anthropometry, percentage of ideal body weight, creatinine-height index, dietary history, subjective global assessment, and – in more sophisticated clinical settings – bioelectric impedance and body composition determinations. Unfortunately, almost all of these tests can be influenced either by underlying liver disease or by factors that may be causing the liver disease, such as chronic alcohol consumption or viral infection. Visceral protein concentrations are probably the tests most frequently used by nutritionists in evaluating nutritional status, especially protein malnutrition. The visceral proteins such as albumin, pre-albumin, and retinol-binding protein are all produced in the liver and correlate better with severity of underlying liver disease than with malnutrition (Merli *et al.*, 1987). Alcohol and viral infection can influence immune function, and edema and ascites can influence anthropometry and bioelectric impedance (O'Keefe *et al.*, 1980; Shronts *et al.*, 1987; Shronts, 1988; Guglielmi *et al.*, 1991; McCullough *et al.*, 1991). Impaired renal function frequently occurs in more severe liver disease and influences indicators such as creatinine-height index (Pirlich *et al.*, 1996). Thus, no ideal single indicator of malnutrition in liver disease exists and, often, subjective global assessment in conjunction with a combination of tests most appropriate for the particular patient will provide the best possible evaluation (Baker *et al.*, 1982; Campillo, 2010). As an example, malnutrition is obvious by subjective global assessment in the alcoholic cirrhotic in Figure 54.1A, and malnutrition has markedly improved with two years of abstinence and appropriate nutrition in Figure 54.1B.

Probably the most extensive studies of nutritional status in patients with liver disease are in patients with alcoholic liver disease (ALD), and we will focus on abnormalities of ALD that can be extrapolated to other forms of liver disease. The best recent studies are two large studies in the Veterans Health Administration (VA) Cooperative Studies Program dealing with patients with alcoholic hepatitis (Mendenhall *et al.*, 1984, 1986, 1993, 1995a,b). The first of these studies (#119) demonstrated that virtually every patient with alcoholic hepatitis had some degree of malnutrition (Mendenhall *et al.*, 1984). Patients (284 with complete nutritional assessments) were divided into groups with mild, moderate, or severe alcoholic hepatitis based on

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