Obesity is a rapidly growing health problem that is associated with more than 65 comorbidities and results in substantially increased all-cause mortality. The increase of obesity has played an important role in the increasing prevalence of nonalcoholic fatty liver disease (NAFLD), the most common cause of liver disease in the United States. Understanding the prevalence, comorbidities, and pathogenesis of obesity provides an essential foundation for clinicians who care for individuals with NAFLD.

Obesity is strongly associated with the prevalence of nonalcoholic fatty liver disease (NAFLD) in adult and pediatric populations. Nutrition, physical activity, and behavioral modifications are critical components of the treatment regimen for all obese patients with NAFLD. Bariatric surgeries that affect or restrict the flow of food through the gastrointestinal tract may improve liver histology in morbidly obese patients with nonalcoholic steatohepatitis (NASH), although randomized clinical trials and quasi-randomized clinical studies are lacking. Early detection of NASH and hepatic fibrosis using noninvasive biochemical and imaging markers that may replace liver biopsy is the current challenge.

Obesity and insulin resistance produce alterations in the liver's normal role in lipid metabolism resulting in a sequence of changes recognizable on liver biopsy. Hepatocellular fat vacuoles increase with BMI, producing steatosis. Steatohepatitis occurs when there is also cytoskeletal damage with loss of keratin filaments, ballooning of affected liver cells and formation of Mallory-Denk bodies. Activation of hepatic stellate cells produces fibrosis in the perisinusoidal spaces. With continuing fibrogenesis there is progression to bridging fibrosis and cirrhosis. Hepatocellular carcinoma may develop in the cirrhotic liver, but both hepatocellular adenoma and hepatocellular carcinoma may occur in pre-cirrhotic fatty liver disease.
also a considerable risk factor for the development of numerous other chronic diseases, such as insulin resistance, type 2 diabetes, heart disease and nonalcoholic fatty liver disease. The epidemic proportions of obesity and its numerous comorbidities are bringing into focus the highly complex and metabolically active adipose tissue. Adipose tissue is increasingly being considered as a functional endocrine organ. This article discusses the endocrine effects of adipose tissue during obesity and the systemic impact of this signaling.

Obesity and NAFLD: The Role of Bacteria and Microbiota

Ajay Duseja and Yogesh Kumar Chawla

There are trillions of microorganisms in the human intestine collectively called gut microbiota. Obesity may be affected by the gut microbiota through energy harvesting and fat storage by the bacteria. Small intestinal bacterial overgrowth is also responsible for endotoxemia, systemic inflammation, and its consequences including obesity and nonalcoholic fatty liver disease (NAFLD). Relationship between gut microbiota and NAFLD is also dependent on altered choline and bile acid metabolism and endogenous alcohol production by gut bacteria. Further evidence linking gut microbiota with obesity and NAFLD comes from studies showing usefulness of probiotics in animals and patients with NAFLD. This article reviews the relationship among gut microbiota, obesity, and NAFLD.

TREATMENT

The Role of Medications for the Management of Patients with NAFLD

Natalia Mazzella, Laura M. Ricciardi, Arianna Mazzotti, and Giulio Marchesini

The article is intended to provide an overview of the strengths and limits of controlled trials of pharmacologic treatment of nonalcoholic fatty liver disease. No drug has so far been approved, although validated on histologic outcomes. Several new drugs are under scrutiny, acting with different mechanisms along the chain of events from fatty liver to fibrosis, cirrhosis, and hepatocellular carcinoma. The article investigates which drug, if any, should be preferred for a tailored intervention in individual patients, according to age, comorbidities, and disease severity, and if treatment should be continued lifelong, to prevent disease progression and long-term occurrence of cirrhosis.

The Role of Diet and Nutritional Intervention for the Management of Patients with NAFLD

Francisco Barrera and Jacob George

During the last few decades, the prevalence of obesity, insulin resistance and non-alcoholic fatty liver disease (NAFLD) have dramatically increased. Nutrition and modern lifestyle habits are intimately involved in this epidemiological change. Although lifestyle intervention can theoretically revert the metabolic disturbances and prevent the long-term complications of NAFLD, its efficacy is diminished in clinical practice by poor implementation and reduced adherence to lifestyle intervention programs. In this article we summarize the main elements of dietary interventions for NAFLD, describe practical strategies to optimize efficacy and review
potential nutritional strategies under development that hopefully will improve outcomes in the future.

Role of Exercise in Optimizing the Functional Status of Patients with Nonalcoholic Fatty Liver Disease

Lynn H. Gerber, Ali Weinstein, and Lisa Pawloski

Nonalcoholic fatty liver disease (NAFLD) is frequently concomitant with obesity. This article discusses factors that influence health and functional outcomes of people who develop NAFLD, including increased burden of illness, whole body function, performance, and perception of self-efficacy. Changes in macronutrients, amount of calories consumed, and decreased physical activity all negatively influence patient outcome. The benefits of exercise in this population are also discussed. To be effective, exercise must be performed, regularly and in conjunction with dietary and other behavioral change. Therefore, a lifelong commitment to exercise, activity, and diet are needed if NAFLD is to be successfully treated.

Surgical Management of Obesity in Patients with Morbid Obesity and Nonalcoholic Fatty Liver Disease

John B. Dixon

Most patients with severe complex obesity presenting for bariatric-metabolic surgery have nonalcoholic fatty liver disease (NAFLD). NAFLD is associated with central obesity, insulin resistance, type 2 diabetes, hypertension, and obesity-related dyslipidemia. Weight loss should be a primary therapy for NAFLD. However, evidence supporting intentional weight loss as a therapy for NAFLD is limited. Bariatric-metabolic surgery provides the most reliable method of achieving substantial sustained weight loss and the most commonly used procedures are associated with reduced steatosis and lobular inflammatory changes, but there are mixed reports regarding fibrosis. Surgery should complement treatment of obesity-related comorbidity, but not replace established therapy.

OBESITY, NUTRITION, AND OTHER LIVER DISEASES

The Impact of Obesity and Metabolic Syndrome on Chronic Hepatitis C

Nicolas Goossens and Francesco Negro

The metabolic syndrome and the hepatitis C virus (HCV) infection are 2 global health care challenges with a complex interaction. Insulin resistance, a central component of the metabolic syndrome, is epidemiologically and pathophysiologically intrinsically linked to HCV infection. Insulin resistance and diabetes affect clinical outcomes in patients with liver disease related to HCV, namely, incidence of hepatocellular carcinoma, liver-related mortality, fibrosis progression rate, response to antiviral therapy, and possibly the incidence of cardiovascular events. Viral and metabolic steatosis and its interactions with HCV and the metabolic syndrome are discussed. Management and the need for further research conclude the article.

The Impact of Obesity and Metabolic Syndrome on Alcoholic Liver Disease

Dian J. Chiang and Arthur J. McCullough

Alcoholic liver disease (ALD) remains a major cause of chronic liver diseases and liver failure. Population-based prospective studies and patient
cohort studies have demonstrated that obesity and the metabolic syndrome exacerbate progression of ALD and increase hepatocellular carcinoma (HCC) incidence and mortality. Emerging evidence also suggests a synergism between alcohol and obesity in mortality and HCC incidence. Recognition of these increased risks and detection of early-stage liver disease may offer the opportunity to address these modifiable risk factors and prevent disease progression in these patients.

The Impact of Obesity and Metabolic Syndrome on Chronic Hepatitis B and Drug-Induced Liver Disease

Ralucia Pais, Elena Rusu, and Vlad Ratziu

Steatosis and insulin resistance (IR) are no more frequent in chronic hepatitis B (CHB) than in the general population. Although experimental studies suggest that the HBx protein induces liver fat, human studies have shown that steatosis and IR are related to coexistent metabolic risk factors, thus epidemiologically linked rather than virally induced. Diabetes and obesity are associated with advanced fibrosis and increased risk of hepatocellular carcinoma in CHB. Despite abundant experimental data showing that fatty liver is more susceptible to liver injury, drug-induced liver disease seems no more frequent in NAFLD patients, except, possibly, a higher incidence but not severity of acetaminophen hepatotoxicity.

SPECIAL TOPICS

Nutrition in Cirrhosis and Chronic Liver Disease

Wassem Juakiem, Dawn M. Torres, and Stephen A. Harrison

Nutrition has not been a primary focus of many medical conditions despite its importance in the development and the severity of these diseases. This is certainly the case with nutrition and end-stage liver disease despite the well-established association of nutritional deficiencies and increased rates of complications and mortality in cirrhosis. This review provides an overview of nutrition in chronic liver disease with an emphasis on its pathogenesis as well as ways to assess nutritional status and intervene in an effort to improve nutrition.

Obesity and Liver Cancer

Ester Vanni and Elisabetta Bugianesi

Obesity is an established risk factor for many types of cancers, particularly for hepatocellular carcinoma (HCC), owing to its carcinogenic potential and the association with nonalcoholic fatty liver disease (NAFLD). HCC may develop in cirrhotic and noncirrhotic livers with NAFLD, particularly in the presence of multiple metabolic risk factors such as obesity and diabetes. This issue is alarming because the population potentially at higher risk is greatly increasing. This review summarizes current evidence linking obesity and liver cancer, and discusses recent advances on the mechanisms underlying this relationship.

Impact of Nutrition and Obesity on Chronic Liver Disease

Vignan Manne and Sammy Saab

Undernutrition and obesity are at opposite ends of a spectrum that has an enormous impact on all aspects of liver diseases. The myriad effects of the
opposing ends of the nutrition spectrum have led to a wealth of research aimed at elucidating the exact mechanisms of how they cause liver damage. In this article, the role of the liver in nutrient and energy metabolism is discussed, as well as the known and possible effects of specific nutrient deficiencies and obesity.

Obesity, Nutrition, and Liver Disease in Children 219
Ariel E. Feldstein, Dana Patton-Ku, and Kerri N. Boutelle

In this article, several aspects of childhood obesity are discussed, including epidemiology, associated metabolic complications, management strategies, and therapy with particular attention to the impact of obesity on the liver, resulting in nonalcoholic or metabolic fatty liver disease. The deleterious effects of obesity on the liver and health overall can be significantly impacted by a culture that fosters sustained nutritional improvement and regular physical activity. The current evidence is summarized supporting pharmacologic, behavioral, and dietary interventions for the management of obesity and fatty liver disease in children.

The Interactions of Nonalcoholic Fatty Liver Disease and Cardiovascular Diseases 233
Hugo Perazzo, Thierry Poynard, and Jean-François Dufour

A complex interaction among metabolic factors, adipose tissue lipolysis, oxidative stress, and insulin resistance results in a deleterious process that may link nonalcoholic fatty liver disease (NAFLD) with severe cardiovascular (CV) outcomes. Patients with NAFLD are at higher risk of atherosclerosis, new onset of CV events, and overall mortality. The strong association between NAFLD and CV disease should affect clinical practice, with screening and surveillance of patients with NAFLD. This review discusses the data linking these major diseases.

Host Genetic Variants in Obesity-Related Nonalcoholic Fatty Liver Disease 249
Rohini Mehta, Aybike Birerdinc, and Zobair M. Younossi

Nonalcoholic fatty liver disease (NAFLD) is a complex disease. The considerable variability in the natural history of the disease suggests an important role for genetic variants in the disease development and progression. There is evidence based on genome-wide association studies and/or candidate gene studies that genetic polymorphisms underlying insulin signaling, lipid metabolism, oxidative stress, fibrogenesis, and inflammation can predispose individuals to NAFLD. This review highlights some of the genetic variants in NAFLD.

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