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REVIEW ARTICLE

Current treatment for non-alcoholic fatty liver disease☆

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KEYWORDS
Non-alcoholic fatty liver disease;
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Abstract Non-alcoholic fatty liver disease is the most prevalent hepatopathy, estimated at 30% in the general population. In the coming years, it will likely be the most common indication for liver transplantation and the most frequent cause of hepatocellular carcinoma. Current treatment for non-alcoholic fatty liver disease is based on dietary and exercise interventions that have been shown to be efficacious, even for reverting fibrosis. Unfortunately, compliance with general measures involving lifestyle modifications is very poor, making pharmacologic strategies a necessary option. At present, there are no treatments for non-alcoholic fatty liver disease approved by regulatory agencies, and the only ones with sufficient evidence and recommended by international societies are treatments with pioglitazone and vitamin E, which are not exempt from adverse effects. We review herein the current management of non-alcoholic fatty liver disease, including dietary and physical activity interventions, available treatments, equivocal therapies, emerging treatments, and treatments presently in clinical trials.
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PALABRAS CLAVE
Enfermedad por hígado graso no alcohólico;
Síndrome metabólico;
Tratamiento

Tratamiento actual de la enfermedad por hígado graso no alcohólico

Resumen La enfermedad por hígado graso no alcohólico es la hepatopatía más prevalente, cercana al 30% de la población general, y se considera será en los siguientes años la indicación más común de trasplante hepático y la etiología más frecuente de carcinoma hepatocelular. El tratamiento actual de la enfermedad por hígado graso no alcohólico se debe basar en las medidas higiénico-dietéticas, que han demostrado ser eficaces incluso para revertir fibrosis.

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Desafortunadamente, el apego a las medidas generales es muy pobre, de ahí la necesidad de contar con estrategias farmacológicas. Hasta el momento no contamos con tratamientos aprobados por las agencias regulatorias para esta entidad, y los únicos tratamientos recomendados por las sociedades internacionales por tener suficiente evidencia son la pioglitazona y la vitamina E, que no están exentas de efectos adversos. En este artículo revisaremos el estado actual del tratamiento de la enfermedad por hígado graso no alcohólico, incluyendo las medidas higiénico-dietéticas, tratamientos disponibles, fármacos equívocos, tratamientos emergentes, y aquellos que actualmente se encuentran en ensayos clínicos.
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Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as a lipid deposit in more than 5% of hepatocytes. It is currently the most common hepatopathy, with an estimated prevalence of 30%.[1] NAFLD is composed of 2 phenotypes: nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH), the latter having a worse prognosis because of its greater risk for progressing to cirrhosis of the liver and for having a closer association with unfavorable outcomes, such as cardiovascular mortality. It is estimated that 20-25% of the patients with NAFLD have NASH, and of those, 20% will progress to cirrhosis of the liver.[2] NAFLD is a spectrum, and patients can pass from having NAFL to NASH, and vice versa, and it is one of the main factors involved in weight changes.[3] On average, progression from one stage of fibrosis to another in patients with NAFL takes 14 years, whereas it takes only 7 years in patients with NASH.[4]

Given the natural history of NAFLD, specific pharmacologic treatments for that pathology should center around NASH, and not NAFL, because there is a low probability of morbidity and mortality due to hepatopathy with the latter.[5] At present, there is no treatment for NASH that has been approved by the regulatory agencies, but hygienic-dietary measures should be at the center of all therapeutic regimens, given their efficacy, even for improving fibrosis.[6] However, as occurs in patients with diabetes or high blood pressure, those measures are not efficacious in the long term in an important percentage of cases due to poor patient adherence. Surgical measures have also been shown to be highly efficacious, but they are not a viable alternative in a disease with such a high prevalence.[7] Therefore, pharmacologic treatment is and will continue to be at the core of management of those patients. In the present review, we focus on current and future pharmacologic treatments, but we also provide a brief discussion of the hygienic-dietary measures, given their great relevance.

Hygienic-dietary measures

Hygienic-dietary measures are very important because they modify disease progression and are usually the basis of treatment of the comorbidities that tend to accompany NAFLD, such as the different components of metabolic syndrome. A limitation to analyzing the effect of diet and exercise on NAFLD is that they are usually accompanied by changes in body weight, making it difficult to interpret results. In addition, most studies focus on the effect on steatosis, but do not have biopsies to determine the effect on the NASH components (inflammation, ballooning) and fibrosis.

Weight reduction

The majority of studies whose aim is to demonstrate the effect of weight loss on NAFLD have a before-and-after design, along with its inherent limitations. A study on 30 patients with paired biopsies showed that a body weight loss greater than or equal to 7% was required for significant improvement in the NAFLD Activity Score (NAS),[8] a scoring system used in pathology that assigns points based on the grades of steatosis, inflammation, and ballooning found in liver biopsy. In a prospective study of 261 patients with paired biopsy, a relation between weight loss results and histopathologic improvement was observed after 52 weeks of lifestyle change: in particular, the necessary weight loss of at least 7% for significant improvement on the NAS (reduction of $\geq$ 2 points) was corroborated. In relation to fibrosis, in that same study, upon losing $\geq$ 7% of body weight, the stage of fibrosis was stabilized in 50% of the patients and there was improvement/resolution in the other 50%. Upon losing $\geq$ 10% of body weight, improvement/resolution of fibrosis was achieved in 80%.[6] From the practical perspective, weight loss of only $\geq$ 3% is required to reduce steatosis, but to achieve resolution of NASH (absence of ballooning), weight loss must be $\geq$ 7%, and to improve fibrosis it must be $\geq$ 10%.

Diet

Any type of diet that results in reduced body weight will have potentially beneficial effects, such as those observed in the weight reduction section. However, an attempt has been made to determine whether the composition of the diet is important in NAFLD, regardless of changes in weight. In a study with a cross-over design that included 12 patients, greater reduction in steatosis, determined

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