

Obesity-related non-alcoholic fatty liver disease (NAFLD): A multifactorial process

The obesity epidemics is a global public health issue. According to the European Commission, the prevalence of overweight and obesity in the European Union member states ranges from 36.9 % to 56.7 % for women, and from 51 % to 69.3 % for men. Obesity and overweight are associated with a wide range of comorbidities, most particularly type-2 diabetes mellitus (T2DM), cardiovascular disease, non-alcoholic fatty liver disease (NAFLD), some types of cancer, and a number of psychiatric disorders (1-3). However, the list of associated conditions may be much longer since obesity has been related to a higher risk of autoimmune diseases and hypersensitivities (4). As a consequence, obesity has a considerable impact on public health systems, a situation that may be aggravated in the near future because of its rising incidence and occurrence at increasingly younger ages.

NAFLD is the liver condition most commonly associated with obesity. NAFLD includes a spectrum of liver disorders ranging from steatosis without inflammation to non-alcoholic steatohepatitis, which in turn is a significant cause of more serious diseases such as liver cirrhosis and hepatocellular carcinoma (5,6); some authors consider NAFLD the source for most cryptogenic cirrhotoses (7). There is a clear relationship between obesity degree and NAFLD prevalence, which may be greater than 80 % in the presence of morbid obesity (body mass index above 40) (8). However, the exact prevalence of steatohepatitis remains unknown, and may change according to the histological criteria considered for its diagnosis. The relationship between liver steatosis and obesity degree is not an absolute one. Recent studies have shown that the prevalence of NAFLD in individuals with overweight or mild obesity is higher than was expected a few years back (8,9); however, between 10 % and 20 % of patients with extreme obesity never develop NAFLD. Obviously, factors unrelated to obesity degree play a role in the origin and outcome of NAFLD.

In the present issue of the *Revista Española de Enfermedades Digestivas (Spanish Journal of Gastroenterology)*, Díez-Rodríguez et al. (10) examine the relationship between Visceral Adiposity Index (VAI) score and NAFLD progression in a cohort of 139 subjects with morbid obesity. From a methodological standpoint, the study offers the benefit of accurate NAFLD diagnosis by histopathology of liver biopsy samples, and also considerable scientific interest, this being the first time that the relationship between VAI and NAFLD histopathology is studied in a cohort with extreme obesity. The authors conclude that Homeostasis Model Assessment (HOMA) index, waist circumference, and presence of metabolic syndrome are all associated with liver histology. However, in a multivariate analysis, VAI scores are associated with the HOMA index scores and metabolic syndrome, but not with liver histology. VAI scores were put forward in 2010 to estimate the risk for cardiovascular disease and type-2 diabetes (11). This index provides a concurrent measure of the amount

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and dysfunction of visceral adipose tissue, and its equation includes, in addition to waist circumference, parameters associated with metabolic syndrome such as triglycerides and HDL-cholesterol. Although VAI was initially associated with liver fibrosis in patients with NAFLD (12), subsequent reports found no association with liver histopathology, specifically a study published in 2012 in the *Journal of Hepatology* in a cohort of 190 patients with NAFLD and 129 control subjects (13). In this setting, the paper by Díez-Rodríguez et al. contributes to detract validity from VAI as a marker of NAFLD progression.

The study by Díez-Rodríguez et al. takes a closer look at one of NAFLD's most interesting aspects: The relationship between fatty liver, adipose tissue, and metabolic syndrome. It is a widely confirmed fact that NAFLD is closely related to excess visceral fat (a phenotype known as central or abdominal obesity) (14,15). Visceral fat is metabolically more active than subcutaneous fat, more liable to change function during obesity, and "closer" to the liver through portal circulation. On the other hand, central obesity extent, as measured with waist circumference, is a mandatory component of current metabolic syndrome criteria (circumference greater than 102 cm in males and 88 cm in females, according to the *International Diabetes Federation*, 2006). The term "metabolic syndrome" was propounded in the 1950s (and became popular during the 1970s) as a conjunction of risk factors for T2DM, and its definition was later extended to include risk factors for cardiovascular disease and fatty liver. While the clinical usefulness of metabolic syndrome has been questioned, it is a fact that obese individuals without metabolic syndrome have a much lower risk of developing cardiovascular disease, diabetes, or NAFLD, which may suggest a common background for the various disorders associated with obesity.

The dual impact hypothesis was posited in 1998 as a model to explain the origin of fatty liver and its subsequent progression to steatohepatitis (16). Lipid overload within hepatocytes (first impact) would trigger a series of cytotoxic events (second impact) ultimately resulting in steatohepatitis. Currently, NAFLD development is deemed a multifactorial process, with changes between patients reflecting both genetic and environmental differences. NAFLD in obese individuals has been linked to several pathophysiological processes, including insulin resistance, leptin resistance, chronic adipose inflammation, and impaired adipokine (hormones and cytokines secreted by the adipose tissue) secretion –increased levels of leptin and proinflammatory cytokines, and reduced adiponectin secretion (17,18). On the other hand, as discussed above, the distribution of fat deposits around the body is determinant, so much so that NAFLD shows an intimate association with obesity (or overweight) phenotypes characterized by a predominance of visceral adipose tissue. These phenotypes, induced by androgenic hormones, are more usual in men (19), which at least partly explains the higher prevalence of fatty liver and steatohepatitis in obese males as compared to obese females.

Most of these pathophysiological processes involve adipose tissue functioning. In this regard, several authors claim that obesity does not give rise to associated disorders for as long as the adipose tissue works properly (20,21). The adipose tissue is now the subject of increasing interest by the scientific community. Indeed, a change of paradigm has taken place in the last few years, and fat tissue has moved from being considered simply a depot of triglycerides to being considered: a) An endocrine organ secreting a wide variety of metabolically relevant molecules; b) an organ with a thermogenic role, following the discovery of thermogenic adipocytes (beige fat) in the white adipose tissue; and c) a tissue with an immune role (22-24). All these roles may become deeply altered during obesity development.

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The expansion limit hypothesis was propounded as a comorbidity mechanism in obese patients, particularly associated with fatty liver development (21). According to this hypothesis, body fat deposits have an expansion limit. This limit is specific for each individual, and depends upon genetic and environmental determinants. When an obese patient approaches his or her expansion limit, lipids are no longer properly stored inside adipocytes, and ectopically overload other tissues, including the liver, muscle, and pancreas. As a result of lipotoxic mechanisms, the liver develops insulin resistance, inflammation, and fibrosis. In support of this hypothesis, adipocyte hypertrophy extent has been associated with T2DM and NAFLD (25,26). Furthermore, recent papers have shown that the adipose tissue of obese patients with diabetes exhibits a variety of infiltrated, activated immune cells (27,28). In fact, chronic adipose tissue inflammation and the release of proinflammatory cytokines into the portal circulation have been thought of as one of the mechanisms connecting central obesity with NAFLD. Finally, we must mention the studies analyzing the influence of the intestinal microbiota of obese patients on obesity-related conditions, which according to some authors impairs intestinal mucosal functioning and determines the severity of inflammation in the visceral adipose tissue (29,30).

In summary, the incidence of NAFLD has considerably increased parallel to the alarming growth of obesity and overweight in developed and a number of emerging countries. There is today considerable interest in understanding the pathophysiological mechanisms underlying the origin and outcome of NAFLD. Recent advances in this area are showing that NAFLD represents a complex multifactorial process with significant differences from an individual to the next that reflect a number of genetic and environmental determinants.

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