Title:
Characterizing specific subgroups in patients with NAFLD: overweight vs obese phenotype

Authors:
Rosa Martín Mateos, Alina M. Allen

DOI: 10.17235/reed.2019.6269/2019
Link: PubMed (Epub ahead of print)

Please cite this article as:

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Characterizing specific subgroups in patients with NAFLD: overweight vs obese phenotype

Rosa Martín-Mateos¹ and Alina M. Allen²


Correspondence:
e-mail: allen.alina@mayo.edu
e-mail: rosam.martinma@salud.madrid.org

Non-alcoholic fatty liver disease (NAFLD) is increasingly recognized as the most common cause of chronic liver disease worldwide, with a global prevalence of 25.2% (1). NAFLD can be categorized into nonalcoholic fatty liver (NAFL), defined as the presence of ≥ 5% of hepatic steatosis without hepatocellular injury in the absence of other competing diagnosis, and nonalcoholic steatohepatitis (NASH), which includes hepatocellular injury and inflammation with or without fibrosis (2). The high burden of NAFLD extends beyond liver disease, as patients are at risk of developing not only liver-related conditions, including cirrhosis and hepatocellular carcinoma, but also cardiovascular complications associated with metabolic syndrome (3).

The present special issue of the Spanish Journal of Gastroenterology (Revista Española de Enfermedades Digestivas) focuses on diverse key aspects of NAFLD, including the characterization of fecal microbiota profiles, the role of bariatric endoscopy, an assessment of suitable pre-clinical models for NAFLD, and the differential epidemiological risk factors associated to NASH and fibrosis.
NAFLD is strongly associated with metabolic syndrome, which includes obesity, hyperglycemia, hypertension and dyslipidemia (4). Obesity prevalence among NASH patients has been estimated over 89% in Europe and 80% in North America (1). However, non-obese subjects are also at risk of developing NAFLD. It has been recently shown that lean patients with NAFLD have an increased risk of all-cause and cardiovascular mortality as compared to lean individuals without fatty liver (5). Conversely, obese people may exhibit no metabolic or hepatic changes, a situation that has been coined as “metabolically healthy obesity”. Therefore, metabolic status rather than body mass index may be the key factor determining risk and outcomes in NAFLD (6).

In the present issue, Dr. R. Aller et al. report the results of an interesting study investigating the differences between overweight and obese patients with NAFLD (7). The study was conducted in 203 subjects (63 overweight and 140 obese) with biopsy-proven NAFLD, with biopsy being indicated for persistently elevated liver enzymes. The prevalence of NASH was higher in the obese group, but there were no significant differences regarding presence of fibrosis or any other single histological parameter. The authors also investigated the proportion of patients carrying the G allele of the patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene, and the A allele of tumor necrosis factor alpha (TNF-α), finding no significant differences in these genetic polymorphisms between groups. Interestingly, adiponectin levels were significantly higher in overweight patients, while resistin and leptin concentrations were increased in obese subjects. Finally, a multivariate analysis found that adherence to a Mediterranean diet was a protective factor for both NASH and fibrosis in overweight patients, and HOMA-IR was found to be only independently associated with the presence of fibrosis in this group.

There are several study limitations that warrant consideration. First, the study included patients with persistently elevated liver enzymes, which prompted the indication for liver biopsy. This study design introduces a bias favoring a more aggressive disease phenotype, with a high probability of NASH; therefore, it is less likely to allow reliable histologic differences between overweight and obese patients in general. Second, studies relying on patient reports of historical dietary intake should be interpreted
with caution because of the risk for recall bias. Lastly, the small number of overweight patients with NASH (n = 26) and clinically significant fibrosis (n = 5) limits study power and multivariate analysis results.

Nevertheless, this study remarks the importance of lifestyle interventions (adherence to a Mediterranean diet) in the management of overweight patients with NAFLD. It would have been of interest to examine whether these risk factors have a similar impact on obese patients in this study’s cohort. Despite huge investment in pharmacological clinical trials, none of the investigated therapies has shown better results than the effect of weight loss as a result of diet and exercise. Significant improvements in the histological features of NASH, and a reduction in hepatic venous pressure gradient may be achieved through lifestyle modifications aimed at losing ≥ 5-10% of body weight (8,9). However, adherence to and long-term maintenance of lifestyle changes may hinder the success of non-pharmacological interventions.

The traditional Mediterranean diet is currently recommended for patients with NAFLD (10), and is characterized by a high content of fresh vegetables, fruits, wholegrain cereals, legumes, and olive oil, as well as a low intake of added sugar and red or processed meat. Adherence to a Mediterranean diet has been shown to reduce the prevalence of metabolic syndrome (11), obesity (12), type-2 diabetes (13), and all-cause mortality in certain populations (14). The findings reported by Aller et al. demonstrate that this dietary pattern is a protective factor for NASH and fibrosis in the overweight group, and are consistent with the current evidence supporting its benefits in patients with NAFLD (15,16).

The PNPLA3 G allele is significantly associated with more aggressive disease in terms of higher liver injury and fibrosis scores when compared to other PNPLA3 alleles (17). Likewise, it has been suggested that TNF-α polymorphisms 208 and 308 are linked to a more severe insulin resistance in NAFLD patients (18). In the present study, the authors did not find significant differences between obese and overweight subjects in the proportions of the G allele of the PNPLA3 gene or the A allele of the TNF-α gene. Data regarding differences between the obese and overweight groups in terms of specific genotypes conferring susceptibility or differential outcomes in NAFLD are scarce. Interestingly, a significantly higher prevalence of the 238 (but not the 308) TNF-
α polymorphism has been found in patients with NAFLD (18). The presence of other significant polymorphisms not analyzed in the present study may be more relevant in differentiating these patients, and further investigations will be needed to elucidate this point.

Finally, different peptides produced by the adipose tissue have been suggested to have an impact on NAFLD. Among them, adiponectin may attenuate liver inflammation and fibrosis, and has been shown to be decreased in patients with NASH (19). Similar findings were observed by Aller et al., who found lower levels of adiponectin in obese patients, the group with a higher prevalence of NASH. On the other hand, leptin and resistin were significantly lower in the overweight group. These adipokines may be related to a more severe phenotype; however, evidence is scarce and warrants further investigation.

In conclusion, the present study demonstrates, in a biopsy-proven cohort of NAFLD patients, that NASH is more prevalent in obese as compared with overweight subjects. In this group, adherence to a Mediterranean diet may protect from fibrosis and NASH, which supports its recommendation for patients with fatty liver disease.

REFERENCES
5. Golabi P, Paik J, Fukui N, et al. Patients with lean nonalcoholic fatty liver disease
are metabolically abnormal and have a higher risk for mortality. Clin Diabetes 2019;37:65-72. DOI: 10.2337/cd18-0026


2017;112:1832-9. DOI: 10.1038/ajg.2017.371


