Therapeutics, Pharmacology and Clinical Toxicology
Vol XXI, Number 2, June 2017
Pages: 47 - 50

A CASE STUDY ON LIFESTYLE AND NUTRITIONAL INTERVENTION IN FATTY LIVER DISEASE

Nițescu Maria[1,2], Săndulescu Oana[1,2], Pițigoi Daniela[1,2], Streinu-Cercel Anca[1,2], Streinu-Cercel A.[1,2]

[1] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[2] National Institute for Infectious Diseases"Prof. Dr. Matei Balș", Bucharest

Abstract. Steatohepatitis is an important concern in patients who are overweight or obese. A 63 year-old male patient presented to our clinic for investigation of asymptomatic low-grade cytolysis. His medical history included ongoing class 2 obesity, arterial hypertension, and metabolic syndrome. Clinical exam showed obesity (body mass index 37.2 kg/sqm, waist-hip ratio 0.97), fatigue, and dyspnea on exertion. FibroMax identified severe steatosis (S3, N1), advanced fibrosis (F3) and important necroinflammatory activity (A3). Steatohepatitis was diagnosed, common viral causes of liver disease were excluded, and a complete nutritional evaluation was performed, with identification of modifiable lifestyle risk factors for fatty liver disease. We designed a personalized lifestyle and nutritional intervention that consisted of a balanced hypocaloric diet of 1800 kcal/day initially and then gradually increased to 2000 kcal/day. The patient was motivated by timely weight loss, disappearance of fatigue and dyspnea, and remained highly adherent to the intervention. At his 8 months follow-up, he had lost 33.5 kg, and the percent body fat had decreased from 35.8% to 20.1%, paralleled by decrease in visceral fat. He had reached a body mass index of 28.2 kg/sqm, a fitness score of 88 points, with normal biochemistry and lipid profile results. FibroMax showed significant improvement, with almost no residual necroinflammatory activity (A0-A1), two-fold decrease on SteatoTest (now at S0-S1), and two-fold decrease in NASHTest (now at N0). The patient will return for follow-up at 12 months. In conclusion, personalized lifestyle and nutritional interventions coupled with achievable targets can be useful in the management of steatohepatitis.

Key words: fatty liver disease; steatohepatitis; physical activity; non-invasive steatosis assessment; bioelectrical impedance

Introduction

Nonalcoholic fatty liver disease (NAFLD) is an important concern in patients who are either overweight or obese, as its evolution can be complicated by progressive liver fibrosis, metabolic syndrome, or concurrent cardiovascular disease [1]. Hepatic steatosis may remain undiagnosed for long periods of time, and may be recognized late, when it is already accompanied by necroinflammatory activity and progressive liver disease. To avoid the important morbidity associated with NAFLD, this condition should be recognized early on, and personalized weight loss interventions should be designed, along with direct counselling regarding all modifiable risk factors for the disease or for its complication.

Săndulescu Oana
National Institute for Infectious Diseases "Prof. Dr. Matei Balș"
1 Dr. Calistrat Grozovici street, Bucharest
e-mail: oana.sandulescu@umfcd.ro

Baseline features

A 63 year-old male patient presented to our clinic in July 2016 for investigation of asymptomatic low-grade elevation of liver function tests, discovered as incidental laboratory finding during routine blood tests. His medical history included ongoing class 2 obesity, essential arterial hypertension, and metabolic syndrome. The family history was unremarkable.

The clinical exam was normal apart for obesity with predominant abdominal distribution (138.6 kg at a height of 193 cm, for a body mass index (BMI) of 37.2 kg/sqm, and a waist-hip ratio of 0.97), fatigue, and dyspnea on exertion.

The patient reported smoking 1 pack of cigarettes/day for a total of 35 years (35 pack-years), and moderate alcohol consumption during the past 40 years (<3 units/day, approximately 3 days/week). He denied all specific risk factors for acquiring viruses with primary

or secondary hepatic tropism. His laboratory tests revealed normal complete blood count and coagulation tests, mild elevation of liver function tests (ALT 164 U/L, AST 79 U/L) without cholestasis, borderline high lipid parameters (Table I), and negative markers for viral hepatitis.

	Baseline	Three months	Eight months
Weight (kg)	138.6	117.3	105.1
BMI (kg/sqm)	37.2	31.5	28.2
Total cholesterol (mg/dL)	233	151	162
HDL (mg/dL)		39	45
LDL (mg/dL)		85	103
Lipids (mg/dL)	757	543	529
Triglycerides (mg/dL)	143	101	74
Fasting plasma glucose (mg/dL)	112	94	93
ALT (U/L)	164	49	34
AST (U/L)	79	31	27
FIB-4	1.88	1.59	1.85
APRI	0.647	0.300	0.290

Table I. Biochemistry panel results

On FibroMax (BioPredictive, Paris, France), severe steatosis was identified, accompanied by advanced fibrosis (F3) and important necroinflammatory activity (A3). Steatohepatitis was diagnosed and as soon as the most common viral causes of liver disease were ruled out, a complete nutritional evaluation was performed, along with identification of modifiable lifestyle risk factors for fatty liver disease through a questionnaire-based interview recording eating habits, physical activity, smoking and alcohol intake. [2, 3] The patient reported irregular eating schedules, with two sizeable meals per day, one in the morning (approximately 1 L of milk) and the other in the evening. His diet sometimes included vegetables, fruits or fish, rarely white meat, and often consisted of red meat (4-5 servings per week) and high fat dairy products (multiple daily servings). He performed little to no physical activity, as his mobility was severely limited by the overall body weight and by dyspnea on minimal exertion.

He had been overweight for the past 16 years. Back in 2000 his weight had been 105 kg (BMI 28.2 kg/sqm), but it gradually increased to 115 kg (BMI 30.9 kg/sqm) by 2005, then to 125 kg (BMI 33.6 kg/sqm) by 2008, and to 137 kg (BMI 36.8 kg/sqm) by 2013, remaining stable for the past 3 years.

A bioelectrical impedance analysis (BIA) was used to assess weight, BMI, skeletal muscle mass, body fat mass and percentage, visceral fat area, waist-hip ratio, and fitness score. At baseline, the patient had a BIA fitness score of 66 points, a visceral fat area of 246 sqcm and a basal metabolic rate of 2293 kcal.

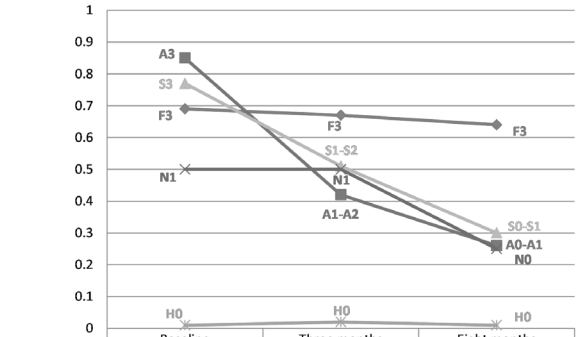
Intervention

After evaluating all modifiable risk factors for obesity and steatohepatitis, a personalized lifestyle and nutritional intervention was designed. The intervention consisted of implementing a regular eating schedule and a balanced hypocaloric diet consisting of 3 main meals and 2 snacks, with daily intake of >5 servings of vegetables/fruits, >3 servings of whole grain cereals and ≥2 servings of low fat milk or dairy, as well as weekly intake of >2 servings of fish, 3-4 servings of lean white meat, and no red meat. The caloric intake was initially set at 1800 kcal/day during the first three months, and was increased to 2000 kcal/day thereafter. The recommended physical activity consisted initially of 30 minutes of strolling each day, gradually increased to 30 minutes of moderate-intensity aerobic physical activity (e.g., fast walking, swimming, gym) each day thereafter. To monitor compliance to the nutritional recommendations and offer periodic personalized reassessments, the patient was instructed to keep a diet diary, recording the number of meals per day, the time, quantity, and type of foods per meal. The diary was sent in for review on a weekly basis and was followed-up by a telephone contact. The patient quit smoking and decreased alcohol consumption from moderate to light intake.

Summary of changes after the intervention

Over the course of the first three months, the patient lost 20 kg (of which 18.6 kg of body fat mass) and reached a BMI of 31.5 kg/sqm. The target weigh loss had been set at 0.5-1 kg/week and therefore the patient was reevaluated to determine the cause of this accelerated weight loss. He had been adherent to the diet, but had increased his physical activity above the recommended amount: during the first month he was unable to perform physical activity, during the second month he started taking 90 minutes walks each day, and during the third month he started going to the gym for moderate to vigorous exercising and swimming for 90 minutes each day. To avoid the risk of liver fibrosis progression following accelerated weight loss, the recommendation to limit the physical activity to moderate intensity and duration was again emphasized. At this three months evaluation, liver function tests had returned to normal, and the metabolic syndrome was no longer present. On FibroMax, NASH remained at the same level, but SteatoTest had significantly decreased by one third. Fibrosis had remained at F3, but the necroinflammatory activity had decreased two-fold, and was now A1-A2 (Figure 1), showing a significant reduction in the overall activity of the fatty liver disease. A concurrent FibroScan (Echosens, Paris, France) evaluated liver stiffness at 6 kPa, suggesting that fibrosis might not be as high as estimated on FibroMax.

The patient was motivated by the timely weight decrease and disappearance of fatigue and exertion dyspnea, and remained highly adherent to the lifestyle and nutritional intervention. At his 8 months (35 weeks) follow-up, he had lost a total of 33.5 kg (of which 28.5 kg body fat mass), he had reached a fitness score of 88 points, with normal biochemistry results, normal lipid parameters (Table I) as well as normal



	Baseline	Three months	Eight months
FibroTest	0.69	0.67	0.64
ActiTest	0.85	0.42	0.26
SteatoTest	0.77	0.51	0.3
NASHTest	0.5	0.5	0.25
ASHTest	0.01	0.02	0.01

Fig.1. Evolution of fatty liver disease as measured by non-invasive assessment of steatosis, fibrosis and necroinflammatory activity

fasting plasma glucose and glycated hemoglobin. The BIA percent body fat decreased from 35.8% at baseline to 20.1% at the 8 months follow-up on BIA, paralleled by an important decrease in the visceral fat (Figure 2). His FibroMax showed significant improvement, with almost no residual necroinflammatory activity (A0-A1), two-fold decrease on SteatoTest (now at S0-S1), and two-fold decrease in NASHTest (now at N0) – Figure 1. FibroMax continued to stage fibrosis as F3 (albeit at 0.64 instead of 0.69) while a concurrent FibroScan (XL probe) and shear-waves elastography on Aixplorer

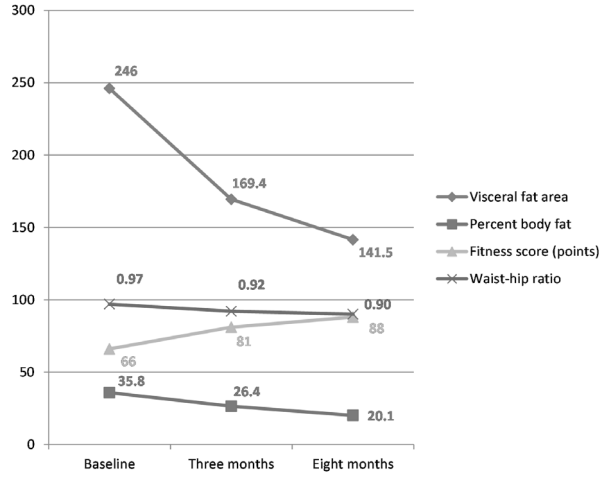


Fig.2. Weight loss dynamics assessed through bioelectrical impedance

(SuperSonic Imagine, Aix-en-Provence, France) yielded a result of 5.2 kPa.

The patient continues to be followed-up regularly in our clinic, and will have his next checkup at 12 months from baseline. In the meantime, he remains highly compliant to both nutritional and lifestyle interventions.

Discussion

The evolution of NAFLD can be complicated by progressive liver fibrosis, potentially leading in time to loss of hepatic function or hepatocellular carcinoma. Vice versa, NAFLD can be an underlying cause for cryptogenic cirrhosis [1], particularly if recognized late. Our patient presented for an accidentally discovered cytolysis, at a point when he already had F3 fibrosis and A3 necroinflammatory activity, and a history of at least 16 years of being overweight/obese.

In this patient, FibroMax (F3) and elastography (F0-F1) had discordant results in terms of liver fibrosis. Both types of measurements remained constant, indicating the same fibrosis stage at different time points, but each placed the patient on a different spectrum of the fibrosis scale. The reason for this discrepancy is probably related to individual variations, and to the distribution of steatosis in the hepatocyte. Certain studies report the risk of overestimating liver stiffness when using elastography techniques in NAFLD [4], but in our case, this was probably an underestimation, which does not come as a surprise, as it is well documented that elastography techniques have important limitations in overweight patients, particularly in patients with increased waist circumference [5]. For F3, transient elastography has a sensitivity of 0.92, meaning that in 8% of the cases fibrosis might be underestimated, and a specificity of 0.70, meaning that in 30% of the cases the values might be overestimated, as shown in a recent Cochrane systematic review [6]. On the other hand, FibroMax has a good performance in discriminating F3 and F4 levels, and is also validated for use in NAFLD, with a nonbinary receiver operating characteristic of 0.878, although the zonal distribution of fibrosis in NAFLD may lead to somewhat lower FibroTest results in certain cases. [7]

Fibrosis is known to occur with long term progression of steatohepatitis, and therefore can be used as an indicator of how advanced the fatty liver disease is. A recent meta-analysis has shown that fibrosis progressed with a mean rate of 0.07 fibrosis stages per year [8]. However, this meta-analysis included mainly patients who were younger, with mean ages around 50 years old. Our patient was 63 years old at the time of diagnosis, and had presented risk factors for steatosis for at least 16 years. Taking into account that an accelerated hepatic aging process can occur in NAFLD (9), all these factors could have contributed to a faster progression of liver fibrosis to an advanced stage such as F3. However, as liver fibrosis has been shown to be a reversible process [10, 11], long term follow-up in our patient might show a gradual decrease of fibrosis now that the steatosis process has been controlled.

There is a general consensus that in obese patients with NAFLD weight loss is the main intervention backed up by good clinical effectiveness [1], however the exact formula to losing weight is less standardized. For this reason, a nutritionist consult is extremely important, in order to be able to provide personalized recommendations [12, 13], substantiated by achievable goals, and close follow-up to ensure good long-term adherence to both lifestyle and nutritional interventions. Physical activity also plays a role in decreasing hepatic steatosis, through an increased muscular demand, regulation of the permeability of hepatocyte membranes, and consequent decrease in hepatocyte fatty deposits.

In conclusion, personalized lifestyle and nutritional interventions coupled with achievable targets can be useful tools in the management of steatohepatitis and should be considered for implementation in multiple hospitals among other individualized healthcare

interventions and, importantly, for earlier management and ideally for prevention of obesity-related complications.

Conflicts of interest: OS was subinvestigator in a clinical trial on non-alcoholic steatohepatitis by Genfit. All other authors – no conflicts of interest to declare.

Consent: Consent was obtained from the patient for the publication of this case study.

Acknowledgement: All authors had equal contributions. This work was supported by the Sectoral Operational Programme Increasing of Economic Competitiveness (POS CCE) (grant number: 1871/49153).

References

1. Sheth S, Chopra S. Natural history and management of nonalcoholic fatty liver disease in adults. *Basow DE, editor. UpToDate. Waltham, MA: UpToDate;* **2017.**

2. Hâncu N, Roman G, Vereșiu I. Diabetul zaharat, nutriția și bolile metabolice. *Cluj-Napoca: Editura Echinox;* **2010.**

3. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation.* **2010;121:586-613**

4. Cournane S, Browne JE, Fagan AJ. The effects of fatty deposits on the accuracy of the Fibroscan(R) liver transient elastography ultrasound system. *Phys Med Biol.* **2012;57:3901-3914.**

5. Castera L, Foucher J, Bernard PH, et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. *Hepatology.* **2010;51:828-835.**

6. Pavlov CS, Casazza G, Nikolova D, et al. Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease. *Cochrane Database Syst Rev.* **2015;1:CD010542**

7. Munteanu M, Tiniakos D, Anstee Q, et al. Diagnostic performance of FibroTest, SteatoTest and ActiTest in patients with NAFLD using the SAF score as histological reference. *Aliment Pharmacol Ther.* **2016;44:877-889**

8. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol.* **2015;13:643-654.e1-9;quiz e39-40**

9. Aravinthan A, Scarpini C, Tachtatzis P, et al. Hepatocyte senescence predicts progression in non-alcohol-related fatty liver disease. *J Hepatol.* **2013;58:549-556**

10. Munteanu M. Biomarker panels and regression of fibrosis in chronic viral hepatitis. *Germs.* **2015;5:115.**

11. Gheorghe L, Rugina S, Dumitru IM, Franciuc I, Martinescu A, Balas I. HLA class II alleles in Romanian patients with chronic hepatitis C. *Germs.* **2015;5:44-49.**

12. Trovato FM, Catalano D, Musumeci G, Trovato GM. 4Ps medicine of the fatty liver: the research model of predictive, preventive, personalized and participatory medicine-recommendations for facing obesity, fatty liver and fibrosis epidemics. *EPMA J.* **2014;5:21.**

13. Rusu E, Enache G, Jinga M, et al. Medical nutrition therapy in non-alcoholic fatty liver disease – a review of literature. *J Med Life.* **2015;8:258-262.**