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PREVENTION AND REVERSION OF NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AMONG OBESE PATIENTS BY MEANS OF CUSTOMIZED NUTRITIONAL AND PHYSICAL ACTIVITY INTERVENTION

Josep Antoni Tur Marí
University of the Balearic Islands

1. Summary

This project has assessed the factors that improve the prevention and/or reversion of non-alcoholic fatty liver disease (NAFLD) in obesity by means of personalized nutritional and physical activity intervention, identifying biomarkers for rapid diagnosis of this disease in future patients.

The relationship of non-alcoholic fatty liver disease to diet, lifestyle, and associated plasma biomarkers has been assessed, as well as to chronic kidney disease, which is associated with non-alcoholic fatty liver disease.

The main conclusions of this study have been: (1) The diagnosis and analysis of the evolution of non-alcoholic fatty liver disease will be usefully facilitated by the measurement of oxidative and inflammatory plasma biomarkers, such as catalase, malonyldialdehyde, cytokeratin-18, superoxide dismutase, irisin, interleukin-6, and resolvin D1. Other useful and applicable elements that contribute to the diagnosis and evolution of the disease are serum ferritin, liver iron, insulin resistance, urinary albumin/creatinine ratio and glomerular hyperfiltration, as well as analysis of liver status by NMR. (2) The key to reversing the fat content of the liver is the practice of regular and regular aerobic physical activity, but not strenuous, although liver tissue will not improve after it has already become fibrotic. The diet, if it is healthy, will help to reverse the disease, as will an adequate and regular night rest period.

2. Obtained results

Relationships between non-alcoholic fatty liver disease and diet:

- The genesis of non-alcoholic fatty liver disease and obesity is related to the pro-inflammatory diet. Therefore, a diet with anti-inflammatory food components will improve and reverse the course of non-alcoholic fatty liver disease.
- The state of non-alcoholic fatty liver can be aggravated by an animal protein-rich diet.
- The composition of amino acids in the diet should be considered in the treatment of non-alcoholic fatty liver disease.
- The stage of the non-alcoholic fatty liver can be improved with a low-fat and slightly

hyperprotein diet of seven intakes a day.

- Animal fat intake and insulin resistance are associated with the urinary albumin/creatinine ratio in patients with non-alcoholic fatty liver disease.
- The state of non-alcoholic fatty liver improves with greater adherence to the Mediterranean diet, mainly due to the antioxidant richness of this diet.
- There is an inverse relationship between nuts consumption and metabolic syndrome and overweight, which are related to non-alcoholic fatty liver disease.

Relationships between non-alcoholic fatty liver disease and lifestyle:

- Patients affected by non-alcoholic fatty liver disease have a short and low-quality sleep, which contributes to the pathogenesis of this disease. Sleep must be added to the behaviours to be modified in the prevention and treatment of this disease.
- The state of non-alcoholic fatty liver improves with the practice of physical activity, adherence to the Mediterranean diet, and the consumption of legumes.
- Non-alcoholic fatty liver disease improves with weight loss, which is associated with changes in the composition of omega-3 fatty acids in the erythrocyte membrane.
- There is a direct relationship between the practice of aerobic physical activity and the involution of non-alcoholic fatty liver disease. It is the key to reversing this disease.
- Fibrosis, once established, does not change despite the dietary and lifestyle intervention that is applied.

Biomarkers of non-alcoholic fatty liver disease:

- Combining routine blood biomarkers and insulin resistance with liver imaging by Nuclear Magnetic Resonance facilitates the diagnosis of non-alcoholic fatty liver disease at an early stage, avoiding more invasive and expensive methods.
- Non-alcoholic fatty liver disease is associated with the gene variant SH2B1 rs7359397, which is enhanced by high intake of animal protein and low intake of monounsaturated fatty acids and fibre.
- Having the T allele of the rs7359397 polymorphism can benefit liver health when prescribing energy-restricted treatment. The benefits are increased if a Mediterranean dietary pattern rich in fibre and omega-3 fatty acids is also observed.
- The severity of non-alcoholic fatty liver disease is related with increased oxidative stress and proinflammatory status, which may be useful in the diagnosis and clinical management of this disease.
- Serum ferritin is a non-invasive marker predictive of non-alcoholic adipose liver

disease.

- High urinary concentrations of resveratrol metabolites improve the lipid profile and serum liver enzymes, and therefore the state of the non-alcoholic fatty liver.
- Plasma biomarkers related to the severity of non-alcoholic fatty liver disease are catalase, malonyldialdehyde, cytokeratin-18, superoxide dismutase, irisin, and interleukin-6; in contrast, resolvin D1 is a plasma biomarker inversely associated with the severity of this disease. Therefore, it can be concluded that the levels of all these biomarkers will serve as obvious indicators of the presence, evolution, and reversion of non-alcoholic fatty liver disease.

Relationship of non-alcoholic fatty liver disease with chronic kidney disease:

- Non-alcoholic fatty liver disease is associated with chronic kidney disease. The most severe stages of non-alcoholic fatty liver disease show higher levels of liver iron, serum ferritin, insulin resistance, urinary albumin/creatinine ratio, and glomerular hyperfiltration.
- Glomerular hyperfiltration may precede chronic kidney disease in patients with non-alcoholic fatty liver disease.
- Renal glomerular hyperfiltration will be reduced by higher energy expenditure (because of more physical activity) by reducing the accumulation of liver fat and insulin resistance.

3. Relevance with possible future implications

- Diagnostics of non-alcoholic fatty liver disease (NAFLD): This study has contributed that the diagnosis and analysis of the evolution and reversion of non-alcoholic fatty liver disease (NAFLD) will be facilitated by the analysis of plasma levels of oxidative stress and inflammation biomarkers related to the disease, such as malonyldialdehyde, cytokeratin-18, superoxide dismutase, irisin, interleukin-6, and resolvin D1. Levels of serum ferritin, liver iron, insulin resistance, urinary albumin/creatinine ratio, and glomerular hyperfiltration will also be useful and applicable, as well as analysis of liver status by NMR.

- Therapy of non-alcoholic fatty liver disease (NAFLD): This study has shown that the key to reversing the liver fat content is the practice of regular and regular aerobic

physical activity, but not strenuous, although liver tissue will not improve after it has already become fibrotic. The diet, if it is healthy, will help to reverse the disease, as will an adequate and regular night rest period.

4. Generated scientific bibliography

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Meeting papers

International: 7; National: 1

PhD Doctoral Thesis

Presented: 4

- Irene Cantero López (2018)
- Bertha Araceli Marín Alejandre (2020)

- Manuela Abbate (2021)
- Nuria Pérez Diaz del Campo (2021)

In progress: 4

- Catalina Maria Mascaró Bestard (started in 2018)
- Sofia Montemayor Frías (started in 2018)
- Margalida Monserrat Mesquida (started in a 2019)
- Maria Magdalena Quetglas Llabrés (started in 2020)