Original article

Mediterranean diet and non-alcoholic fatty liver disease
The need of extended and comprehensive interventions

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SUMMARY

Background & aims: Non-alcoholic fatty liver disease (NAFLD) is mostly related to increased BMI and sedentary life, even if it not directly attributable only to these or to single specific factors. Unhealthy lifestyle and obesity are the most probable causes, also in non-diabetic and without alcohol abuse patients, even if lean individuals can be involved. NAFLD treatment is currently warranted and driven by comprehensive lifestyle intervention, a valuable objective that is more often wished for than actually achieved. The aim is to re-assess the effectiveness of an intervention focused to increase the Adherence to Mediterranean Diet Score (AMDS) and the level of physical exercise, investigating the factors associated with failure and reporting the time that must elapse before such intervention becomes effective.

Methods: The study included 90 (F 46, M 44) non-alcoholic non-diabetic patients, aged 50.13 ± 13.68 years, BMI 31.01 ± 5.18 with evidence of fatty liver by ultrasound.

Results: A significant decrease of Bright Liver Score (BLS) was observed only after 6 months of intervention: differently, at the first and third month of monitoring fatty liver changes were still not significant. By a multiple linear regression model Adherence to Mediterranean Diet change (p:0.015) and body mass index changes (p:<0.0001) independently explain the variance of decrease of fatty liver involvement (R² = 0.519; p < 0.0001).

Conclusion: Adherence to Mediterranean Diet is a significant predictor of changes in the fat content of the liver in overweight patients with NAFLD. The effect of the diet is gradual and favorable and it is independent of other lifestyle changes.
practice; those with evidence of fatty liver by ultrasound (US), graded 0–3 according to the Bright Liver Score (BLS). Three statistical Analysis. BLS, Adherence to Mediterranean Diet (MD) and physical activity were assessed by HOMA-IR, BMI and AMDS. Adherence to Mediterranean Diet intervention (6 months), based on cognitive-behavioral strategies, included goal setting, self-monitoring, feedback and reinforcement, self-efficacy enhancement, incentives, modeling, problem solving, relapse prevention, and motivational interviewing. The measurable goal was the increase of Adherence to Mediterranean Diet Score (AMDS; range 0–55) and reducing sedentary habits, assessed by detailed physical activity reports (Baecke tool). Monthly scheduled clinical, laboratory and dietary controls were provided with the goal of reducing grade and prevalence of liver steatosis in these patients. Self-monitoring has a key role for enhancing individual awareness of daily lifestyle habits and areas where these behaviors conflict (or concur) with desired behavior, and includes simple strategies, mostly handwritten diaries for the record of positive lifestyle change. Behavioral counseling is provided by healthcare professionals, physician, dietitian, health psychologist, trained to tailor the message to the individual’s particular needs. Statistical Analysis. BLS, Adherence to Mediterranean Diet Score, physical activity, assessed by the Baecke tool, insulin resistance assessed by HOMA-IR and BMI changes were compared by repeated measures ANOVA and, subsequently, also by paired Student’s t test at one, three and six month after the intervention vs. the initial measurements. The changes (Δ) of these last measures were challenged by a multiple linear regression (MLR) model against the changes of BLS (ΔBLS) to find predictive independent effect(s), if any, at one, three at six months of follow-up. The lower quartiles, i.e. the 25th percentiles of the measurement changes (ΔBMI, ΔHOMA-IR, Δphysical activity, ΔAMDS), which indicate failure of achievements of the goals at the sixth month of intervention, were calculated and used to describe the association of these smaller and not satisfactory measurement changes with the failure to improve NAFLD as assessed by ultrasound BLS; these data are presented as Odds Ratio (OR) and 95% confidence interval (CI).

3. Results

The study included at last 90 (F 46, M 44) non-alcoholic fatty liver disease (NAFLD) non-diabetic patients; they were aged 50.13 ± 13.68 years; 36/126 patients were excluded due to the lack of the preliminary criteria of inclusion. Results are summarized in Table 1. Body mass index was initially 31.01 ± 5.18. Significant decrease of BMI was observed from the first month of intervention; significant decrease of HOMA-IR was observed only after three and six months, and not at the first month. Significant increase of adherence to Mediterranean Diet and increase of physical activity were observed at the first month, with further gradual increments in the following periods. A significant decrease of BLS was observed only after 6 months of intervention: differently, at the first and third month of monitoring fatty liver changes were still not significant; no significant change of transaminases was observed throughout the study, provided that the baseline values were already within the normal range, according to the selection criterion. By a Multiple Linear Regression age balanced model, Adherence to Mediterranean Diet change (p<0.015) and BMI changes (p<0.0001), independently from the changes of the other predictors, challenged concurrently [ΔPhysical Exercise (p: 0.749, ns) and ΔHOMA-IR (p:0.164, ns)], explain the variance of decrease of fatty liver involvement (R² = 0.519; p < 0.0001). This effect of Adherence to Mediterranean Diet change is significant only at the sixth month, and no earlier predictive effect is observed challenging the model at the first and the third month. After one year of observation, without further pro-active counseling, the achieved results were maintained: BMI 29.41 ± 3.26; HOMA 2.36 ± 1.34; BLS 1.04 ± 0.60; AMDS 35.16 ± 3.18; Baecke score 43.88 ± 6.98; ALT 18.36 ± 9.47. Using the Odds Ratio, the unfavorable factors associated with failure of NAFLD improvement were minor AMDS change, minor BMI decrease, minor physical exercise score increase and smaller HOMA-IR (insulin resistance) decrease (Fig. 1).

4. Discussion

It was recently reported that even after remarkably short periods of time of intervention (two weeks), readdressing diet within healthier boundaries focusing on the Mediterranean Diet is an effective and affordable strategy against NAFLD. Despite this result is quite surprising, a possible explanation is that such study

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Change of measurements after Mediterranean diet comprehensive intervention – repeated measures ANOVA</th>
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</thead>
<tbody>
<tr>
<td>Base</td>
<td>1st month</td>
</tr>
<tr>
<td>BMI</td>
<td>31.02 ± 5.18</td>
</tr>
<tr>
<td>HOMA</td>
<td>3.23 ± 1.36</td>
</tr>
<tr>
<td>BLS</td>
<td>1.96 ± 0.69</td>
</tr>
<tr>
<td>AMDS</td>
<td>27.46 ± 3.74</td>
</tr>
<tr>
<td>BAECKE</td>
<td>38.87 ± 3.95</td>
</tr>
<tr>
<td>ALT</td>
<td>23.33 ± 9.62</td>
</tr>
</tbody>
</table>

*p<0.05; **p<0.001; ***p<0.0001; n=90.

Fig. 1. Factors associated with failure of improvement of NAFLD in non-diabetic patients, after having provided a 6 months intervention by nutritional and comprehensive lifestyle counseling. Minor increase of Adherence to Mediterranean Diet profile score (ΔAMDS, LR 1.235; 95% CI 0.510–2.994), minor BMI loss (ΔBMI, LR 13.333; 95% CI 4.865–36.541), minor increase of Baecke physical exercise score (ΔPhysical Exercise, LR 7.556; 95% CI 2.885–19.784) and minor decrease of insulin resistance (ΔHOMA-IR, LR 1.545; 95% CI 0.644–3.599) are the factors associated with greater likelihood of failure of intervention at six months.
was performed in cohorts of subjects within a nutritional culture very far from the Mediterranean Diet profile, so that such an exceedingly quick effect on liver histology, with complete disappearance of hepatic steatosis, could be the consequence of this steep dietary change. Actually, moderate calorie restriction causes early temporal changes in liver and skeletal muscle metabolism so that 48 h of calorie restriction affects the liver (triglycerides content, hepatic insulin sensitivity, and glucose production)\(^1\): nonetheless, the situation is probably different in current clinical conditions as was in our study. Our experience, and the results of the present study performed in a selected group of patients (non-diabetics, no alcohol, good adherence to dietary prescriptions), supports a less straightforward conclusion. We actually observe only after six months, in a population still within the culture of Mediterranean Diet, with a comprehensive and pro-active lifestyle intervention, a late but significant improvement of the severity of bright liver in NAFLD. This was achieved by a clinical strategy including also the enhancement of habitual physical exercise, whose changes were significant earlier, beginning with the first month. Insulin resistance is still very relevant at the third month, when fatty liver by US imaging is still present. BMI changes, even significant, are almost minimal, confirming that the qualitative profile of the dietary intervention is seemingly responsible of the benefits, while the concurrent weight loss is almost negligible. The question is if the enhanced Adherence to Mediterranean Diet is a significant predictive factor for NAFLD resolution and fatty liver improvement. In the chosen model only AMDS change is, at the sixth month, the factor that explains, alone, fatty liver decrease concurrently with BMI decrease. This last has an independent behavior, as independent are insulin resistance decrease and physical activity increase; these two last are, nonetheless, not sufficiently significant predictors. Several studies have documented an inverse association between adherence to the Mediterranean Diet and risk of coronary heart disease, stroke, cognitive decline and all-cause mortality; it is argued, conjecturally, that this comprehensive nutritional profile, whose rational support is based mainly on epidemiological information, is beneficial.\(^1\) In a less severe frame of disease, the relevance of effects of insulin resistance on the natural history of NAFLD are demonstrated as an independent determinant for future development of non-alcoholic fatty liver disease during a 5-year follow-up in nondiabetic healthy adults.\(^12\) Nutritional intake profile, intestinal flora, gut permeability and the development of NAFLD are demonstrated to be related in humans: permeability, endogenous alcohol synthesis, and endotoxin levels in plasma were significantly higher in patients with NAFLD than in controls.\(^13\) A recent review\(^14\) and another researches suggest, as we do, that Adherence to the Mediterranean diet is associated with the severity of non-alcoholic fatty liver disease,\(^15\) if not with its lower prevalence, and that other mechanisms could be operating, including the possible beneficial effects of the Mediterranean diet on non-alcoholic fatty liver disease mediated by reduced iron stores\(^16\) and by interaction with renal and endocrine function.\(^17\)

Probably human microbiome dietary modification in humans,\(^18\) along with a more in deep focus on dietary profiles and on physical exercise,\(^18–21\) instead of on single nutrients or food, could contribute to explain the mechanism by which “healthy diets” are effective not only in the prevention but also in the clinical treatment of NAFLD and other related conditions.

4.1. Conclusion

Benefits of a greater Adherence to Mediterranean Diet for the liver are, at least in NAFLD, a gradual and slow favorable process.

Conflict of interest

Each author contributed significantly to the study and all authors had access to the data and a role in writing the manuscript. No relevant conflict of interest was present for any of the authors.

Acknowledgements

All persons gave their informed consent prior to their inclusion in the study as a part of the comprehensive informed statement of consent to the anonymous use of sensitive data. No relevant or potential conflict of interest is present for any of the Authors.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2014.01.018.

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