Cognitive-Behavioral Treatment of Non-alcoholic Fatty Liver Disease: A Propensity Score-Adjusted Observational Study

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Abstract

The effectiveness of cognitive-behavior treatment (CBT) in nonalcoholic fatty liver disease (NAFLD), largely related to overweight/obesity and considered the hepatic expression of the metabolic syndrome (MS), has so far been tested in very limited samples. In a tertiary referral center, consecutively-observed NAFLD subjects were offered a CBT program aimed at weight loss and increased physical activity, based on 13 group sessions; 68 cases entered the treatment protocol, those who refused (n=82) were given recommendations for diet and physical activity. Treatment goals (weight loss ≥ 7% initial b.w., normalization of liver enzymes and improved parameters of MS) were tested by logistic regression at 6 months (all cases) and at 2 years, both on intention-to-treat (ITT) and in completers (Diet, 78; CBT, 65). The results were adjusted for the propensity score of attending the CBT program, based on civil, anthropometric and clinical variables. At baseline the CBT group had a larger prevalence of obesity and more severe insulin resistance (HOMA assessment). At follow-up, CBT was associated with a higher probability of weight loss and normal liver enzymes (6-month: odds ratio (OR), 2.56; 95% confidence interval (CI), 1.15-5.69; 2-year ITT: OR, 3.57, 95% CI, 1.59-8.00), after adjustment for propensity and changes in body weight. A similar trend was observed in the outcome goals of insulin resistance and the score of MS, which were both reduced. In conclusion, subjects with NAFLD participating in a CBT program significantly improve their general and liver parameters. The beneficial effects are largely maintained at 2-year follow-up, in keeping with the lifestyle-related pathogenesis of disease.

Introduction

Nonalcoholic fatty liver disease (NAFLD), now considered the hepatic expression of the metabolic syndrome (MS) (1), represents the most common cause of altered liver enzymes (2), namely alanine aminotransferases (ALT), which constitutes the first-level diagnostic tool for hepatic steatosis, together with bright liver at ultrasonography (3). The increasing prevalence of NAFLD in the general population has close associations with the global epidemics of obesity and diabetes (4), which are also linked to more severe fibrosis and increased risk for liver-related morbidity and mortality in subjects progressing to nonalcoholic steatohepatitis (NASH) (5). The high prevalence of associated metabolic disorders and additional features of MS explains why patients with NAFLD are also at significant risk for cardiovascular disease (6), which in most series dictates prognosis more than liver disease progression. Consequently, attempts at finding effective treatments have taken a similar course as other obesity-related chronic diseases and traditionally involve weight reduction and medical management of cardiovascular risk factors with the aim of removing steatosis and preventing fibrosis progression. Weight loss programs including diet (7), nutritional counseling (8), anti-obesity and insulin sensitizing drug therapy (both metformin and glitazones)(9) and bariatric surgery (10) have all been trialed. With the exception of surgery, promising short-term effects are followed by disappointing results in the long term (11) or when drug is discontinued (12).

Despite the recognized benefits of weight reduction, maintaining weight loss in clinical practice is difficult. Structured programs of cognitive-behavioral treatment (CBT) have been advocated to improve adherence (13), but their effects have been tested only in very limited groups and the methodology of intervention is usually scarcely defined (13). Their usefulness has been validated within research settings in metabolic diseases (14-16), also outside research centers (17). CBT is designed to adopt a holistic approach to lifestyle intervention incorporating improvements to dietary intake and physical activity through multi-disciplinary behavior change models. The equal importance of physical activity and psychological strategies to maintain new behaviors is expected to have additional effects on blood lipids, liver fat and cardiovascular risk, compared to what is expected with dietary prescription alone. A one-year randomized controlled study involving only 31 patients has recently demonstrated a beneficial effect of CBT on histological outcomes in NAFLD (18).

The present observational study is based on an audit of service delivery in standard practice, aimed at defining the effects of a structured program of CBT on obesity, cardiovascular risk

factors and liver enzyme levels, in a large cohort of subjects attending a referral center for NAFLD. Data were analyzed by procedures that provide statistical significance to the results.

Materials & Methods

A total of 176 NAFLD patients attended our tertiary referral outpatient department for treatment during the period January 2005 - December 2007. Twenty-six (14.7%) did not return for the scheduled diagnostic work-up appointments and were not considered. We report data on the remaining 150 cases (Table 1) who, at time of analysis (June 2010), had completed a 2-year follow-up and whose data had been registered at 6 months (short-term, n=150), 12 months (medium-term, n=145) and 2 years (long-term, n=143; CBT, 65 cases; Diet, 78). Since 2005, all subjects referred to the unit of Clinical Dietetics because of raised liver enzymes and sonographic evidence of fatty liver have had an extensive evaluation of their metabolic profile, including an oral glucose tolerance test in the absence of overt diabetes. According to a pre-defined protocol, during the first visit they receive detailed information about the long-term risk of advanced liver disease and meet a dietician, who performs a structured interview on their dietary pattern and on the past and recent history of body weight and physical activity. At the end of the diagnostic work-up, all subjects are invited to participate in a cognitive-behavioral treatment (CBT) program aimed at lifestyle changes (see below), following a motivational interview. The patients are informed about the group nature of the program, the duration of the weekly meetings and its total length, and the potential barriers to group sessions are explored to reduce later dropout. All subjects who refuse the CBT program receive a moderately restricted diet, tailored on individual preferences, and general guidelines for physical activity. According to our protocol, liver biopsy is usually postponed (by at least one year), depending on the time-course of liver enzymes.

Follow-up visits are scheduled at 3 months (end of CBT) and 6 months in subjects enrolled into the CBT program and at 1, 3 and 6 months in patients who receive the tailored diet, to monitor body weight, the metabolic profile and to reinforce motivation for weight loss. All subjects are then seen every 6 months to promote maintenance of weight loss and to strengthen adherence to increased physical activity.

Metformin was the first-line treatment in all subjects with overt diabetes (n = 43; 21 in the CBT group, 22 in the Diet arm), with glyclazide (6 cases), repaglinide (2 cases) or glitazones (only 2 cases intolerant to metformin) as second line. The glucose-lowering treatment with

metformin or glitazones was maintained unchanged throughout the study period, whereas the treatment with insulin secreting agents was reduced and eventually stopped according to weight loss and improved metabolic control.

All subjects signed an informed consent to data collection and analysis. The plan of the present report was approved by the Senior staff committee of the Department, an Institutional Review Board regulating non-interventional studies.

Cognitive-behavioral program

Our CBT program is delivered during 13 weekly sessions, 120 min each, supported by a residential manual based on the principles of LEARN program for weight control. Group sessions (approx. 15-20 subjects), chaired by physicians, dieticians, psychologists, communication experts and physical trainers, integrate education with cognitive behavioral procedures and strategies. Education addresses the following main topics: a) energy balance; b) the alimentary pyramid, size of portions and regular eating; c) calorie counting; d) shopping and food labels; e) physical activity, when and how much. Cognitive behavioral procedures and strategies include: a) self-monitoring of food intake and body weight; b) stimulus control strategies; c) problem solving; d) cognitive restructuring of dysfunctional thoughts that obstacle weight loss; d) relapse prevention

Upon entering the CBT program, the patients cease any prescriptive diet they might have followed in the past, and start with a self-managed, nutritional plan.

Measures

Body weight and height, waist circumference and blood pressure were measured as previously reported (1). Body mass index (BMI) is weight (kg) divided by height $(m)^2$. A 7% decrease in body weight was selected as outcome measure considering that this value was also the chosen target in the Diabetes Prevention Program (14), the Look AHEAD study (19) and in the trial comparing CBT with standard nutritional treatment in NASH (18).

The measurement of plasma glucose, total cholesterol, HDL-cholesterol, triglycerides and liver enzymes (aspartate and alanine aminotransferase - AST and ALT) were measured with routine assays using internal and external quality controls. Insulin resistance was calculated according to the homeostasis model assessment (HOMA) method (20), on the basis of glucose and insulin concentrations.

The diagnosis of type 2 diabetes and prediabetes (impaired fasting glucose (IFG)) was based on history and on biochemistry at the time of the first visit, according to the criteria of the World Heath Organization (21). The diagnosis of MS was made on the basis of three or more of the criteria of National Cholesterol Education Program-Adult Treatment Panel III (ATPIII) (22), recently harmonized with the criteria of the International Diabetes Federation (23).

Physical fitness was tested in a population sub-sample by the calculation of oxygen consumption (VO_2max) on a treadmill (RunRace, Technogym, Gambettola (FC), It), during three 5-min stages of exercise at graded heart rate (55%, 60% and 65% of maximal theoretical heart rate). VO_2max was extrapolated by regression to maximum heart rate.

In all cases the percent of steatosis was estimated by means of an algorithm, based on clinical and biochemical parameters (presence of MS and type 2 diabetes, fasting insulin, AST and AST/ALT ratio), recently validated against proton magnetic resonance of the liver (24).

Sample size

According to our previous experience, approximately 25% of cases normalize liver enzymes in the short term, following a prescriptive diet. To be meaningful for clinical purposes, we considered that CBT could double the probability of normal liver enzymes (50% of cases). Accordingly, at least 50 cases per group were needed, considering an α error of 0.05 and a β error of 0.2, and a drop-out rate of 20%. An interim analysis was carried out when this number became available in the CBT arm at the 2-year follow-up and was repeated when all cases reached the 2-year follow-up.

Statistical analysis

Data were extracted from the general database using specific subroutines and were analyzed per protocol using StatView 5.0™ (SAS Institute Inc., Cary, NC.) and SPSS v11.0.4 (SPSS Inc., Chicago, IL). Unpaired t-test (2-tail), chi^2-contingency test and Fisher's exact test were used, whenever appropriate, to test differences in baseline values. Both an intention-to-treat (ITT) and a per-protocol analysis was carried out on the time-course of biochemical and clinical data by means of repeated-measures, time x treatment ANOVA. The last-observation-carried-forward (LOCF) technique was used to complete the dataset in subjects missed at follow-up after 1 year. Considering that missed data were < 5%, only the ITT analysis is reported in text, tables and figures (no differences compared with the per-protocol analysis).

To adjust for baseline differences between groups, a propensity score analysis was used. The propensity score was calculated by logistic regression analysis; it defines the probability to adhere to the structured program, compared to subjects given the prescriptive diet, on the basis of at baseline. The propensity score does not only define the conditional probability to accept a specific treatment given clinical and biochemical individual characteristics (BMI, ALT, individual features of MS), but also includes variables which constitute potential barriers to CBT group treatment. In particular, age, sex, marital status, educational level, occupation, distance from the CBT center were considered (see Table 1). The last two variables are intimately linked to time constraints and to the economic burden of the program.

The propensity scores were then used to adjust for baseline values in logistics regression analysis in 5 different models, having weight loss, ALT normalization, HOMA-IR values below the 75° percentile of normal (2.7%)(25) and a reduced score of MS as the dependent variables. Values were also corrected for changes in percent BODY WEIGHT during the observation period. Two upper limits of ALT were considered as dependent variables: 1) the standard values used in our Departments (40 U/L) and 2) an updated definition of healthy ranges, (<31U/L men; <19U/L women) proposed in 2002 (26).

Further, we checked the validity of our model testing the association between treatment group and target ALT in a subset of matched cases. For this purpose, the whole database was ordered for propensity score, and each subject treated by CBT was pair-matched with a case treated by prescriptive diet. To achieve a perfect matching, only the 5 cases preceding or following the index case in the list were considered. Using this criterion, we could match 43 CBT-treated cases. Subsequently, the association of the CBT program with treatment outcomes was reassessed in this cohort by logistic regression, after adjustment for propensity and percent body weight, as needed.

Data in text and in tables are given as means ± standard deviation or as median (interquartile range – IQR), due to non Gaussian distribution. The significance level was set at $P < 0.05$.

Results

Baseline characteristics

Compared to subjects who limited the intervention to the prescriptive diet, the subjects entering the CBT program were more frequently females, with a larger proportion of housewives, employed and retired people; they also had a higher BMI and higher insulin resistance (**Table 1**). Among the features of MS, the CBT group had a very high prevalence

of waist circumference exceeding the ATP-III cut-off (90% vs. 56%; p < 0.001, **Figure 1**), without significant differences in the prevalence of other criteria or in the overall prevalence of MS (71% vs. 66%; p = 0.600).

At baseline, the prediction algorithm proposed by Kotronen et al (24) identified NAFLD in 139/150 cases at the sensitivity cut-off of 86% (> -0.640). The 11 missing cases were 7 in the diet group, 4 in the CBT program. The estimated percentage of liver fat was similar in the 2 groups (diet, 10.9 ± 6.2% vs. 12.2 ± 7.3 in the CBT group; P = 0.231), and above the estimated cut-off value of 55.6 mg triglyceride/g liver tissue in 128 cases (68 (83%) in the diet group, 60 (88%) in CBT), without differences between groups (P = 0.488).

Effects of treatment

Only 7 cases (4 in the Diet group, 3 in the CBT group) were lost to follow-up in the period between 6 months and 2 years from entry into the study. In response to treatment, a significant percent reduction of body weight was observed in the CBT group after 6 months (median, -4.8%; interquartile range (IQR), 5.8), which was even larger at 2 years (median, -5.6%; IQR, 7.0)(P vs. baseline, < 0.001 for both). The changes observed in the prescriptive diet group were also statistically significant, but remarkably lower, both at 6 months (median, -1.8%; IQR, 5.3; P < 0.001) and at 2 years (-1.4%; IQR, 6.3; P = 0.004) (**Figure 2**).

Average fasting glucose levels progressively decreased during follow-up, to 100 mg/dL in the CBT group and to 101 mg/dL in the Diet group at 6 months, to 99 and 100 mg/dL at 12 months and to 98 and 101 mg/dL at 2 years, respectively, without differences in the two groups. By contrast, the changes in HOMA were more marked in the CBT group. At 6 months HOMA levels in the CBT cases were no longer different from those observed in the Diet group and continued to decline throughout the observation period (**Figure 2**).

Both AST and ALT were reduced during follow-up. The CBT group demonstrated a significantly greater decrease in ALT compared to diet prescription. Within 6 months the average ALT was under the normal threshold in the CBT group but not in the diet group (38.6 ± 15.5 vs. 59.6 ± 31.8 mU/mL p<0.001) and this was maintained throughout the following 2 years (35.5 ± 15.0 vs. 51.8 ± 26.8 p<0.001)(**Figure 2**). At 6 months, the prevalence of cases with ALT levels within the normal range was 60% in the CBT group and 30% in the Diet group (P < 0.001, Fisher's exact test). The difference was maintained at 2 years (62% vs. 38%; P < 0.001).

All these changes were accompanied by a remarkable improvement in the other features of MS (namely blood glucose, HDL-cholesterol and triglycerides, mainly in the CBT group – not reported in details). In particular, glyclazide treatment was reduced (one case) or stopped (one case) in two of the 3 CBT cases with diabetes in the course of the 2-year follow-up, whereas it was maintained in the 3 cases treated by prescriptive diet.

Determinants of changes

In the first logistic regression model (**Table 2**), we tested the association of the treatment program with the achievement of significant weight loss (defined as >7% b.w.). In both the short (6 months) and long (2 years) term, the CBT program was more effective than diet, with those in the CBT group 2.53 times more likely to maintain this weight loss target at 2 years compared to those in the diet group.

In the second model adjusted for propensity, ALT levels within normal values (<40mU/ml) were significantly associated with participation in the CBT program and this favorable effect was maintained after further adjustment for changes in body weight. The results of the sensitivity analysis using the updated lower healthy ALT cut-offs (26) did not differ significantly (not reported in details). The participation in the CBT program increased the probability to reach the targets in the short-term, but at 2 years the association with the lower healthy cut-offs was no longer maintained after adjustments.

In the third model having HOMA-IR < 2.7 as outcome, after adjustment for propensity the subjects in the CBT group were several times more likely to achieve the target, compared to the diet group at 2 years. The modeling showed that this association was not solely accounted for by the greater decrease in body weight following CBT.

Finally, in the fourth model having changes in the score of MS as dependent variable, participation in the CBT program increased the probability of reducing the score by at least 1 point, but adjustment for weight loss cancelled out the significance.

The exclusion of the 11 cases who were not classified as NAFLD on the basis of the predictive algorithm (24) did not change the results of the various models (not reported in details).

Pair-matched analysis

These results were confirmed by the analysis of 43 pair-matched cases having similar propensity levels. The average propensity score was 0.50 ± 0.19% in the CBT group and 0.52

± 0.19 in the Diet group (P = 0.732). At two years, CBT treatment was associated with a much higher probability to maintain weight loss > 7% (odds ratio (OR), 2.92; 95% confidence interval (CI), 1.12-7.57; P = 0.028). In addition, the subjects in the CBT group were much more likely to have ALT levels within the normal range (OR, 3.09; 95% CI, 1.20-7.93; P = 0.019) as well as HOMA-IR < 2.7 (OR, 6.99; 95% CI, 1.75-27.98; P = 0.006) and a reduced MS score (OR, 2.95; 95% CI, 1.08-8.02; P = 0.034), after adjustment for both propensity score and changes in body weight.

Physical fitness

The evaluation of physical fitness was carried out in 29 patients (16 in the diet group, 13 in the CBT sample) at baseline and after 6 months. Their entry clinical and laboratory values were not statistically different from those observed in the total sample. In particular, the BMI was 34.0 ± 6.2 kg/m^2 and 28.9 ± 5.8 in CBT and diet, respectively (P = 0.031). At baseline, physical fitness was moderately lower in subjects entering the CBT program (VO_2max, 27.0 ± 5.7 mL/kg/min, compared with those in the diet group (31.1 ± 5.2; p = 0.052). After 6 months, the values of the two groups were perfectly similar (32.0 ± 7.1 mL/kg/min in the CBT and 31.2 ± 5.5 in the Diet group), due to a significant improvement only observed in the CBT group (+5.0 ± 3.7 mL/kg/min; p vs. baseline, < 0.001).

Discussion

The study shows that a CBT program managed within a tertiary referral centre is associated with a larger weight loss and a significant improvement in insulin sensitivity and in liver enzymes in subjects with NAFLD, compared with a standard dietary prescription. The beneficial effects partly extend to the features of MS in a relatively long-term follow-up.

CBT has been extensively investigated in metabolic diseases, namely in obesity (27), in subjects at risk (14, 15) or with overt diabetes in the community (28), as well as in subjects with mild hypertension to prevent progression to organ disease (16). In all cases, CBT was effective, and possibly more effective and long-lasting than drug treatment. The association between NAFLD and MS was the reason why we tested CBT in our patients, and the results were consistent with those in other associated conditions. Our study lends support to a seminal experience in a general population of obese subjects with liver disease (29), where CBT showed beneficial effects on liver enymes.

The strength of this study is the availability of data on consecutive subjects who agreed to participate to the CBT program, thus reflecting the "real world" hospital care of NAFLD cases. The low drop out rate of 14% (26/176) reduces the confounding effect of attrition which often occurs in weight loss studies. Clinical data of dropouts were not different from those observed in subjects who agreed to follow-up (data not shown).

The majority of subjects were compliant to long-term follow-up, particularly subjects entering the CBT program, where the regular contact with therapists and clinicians may help maintain motivation and compliance with lifestyle changes, and facilitate weight loss and weight-loss maintenance (27). All cases were highly motivated to change their lifestyle when first seen for their elevated liver enzymes, steatosis and associated metabolic diseases. The participation in the CBT program was however hindered by individual barriers to group attendance, which were partly explored at interview (marital status, job-related time constraints and loss of income, living far from the center), limiting the applicability of CBT to the whole group of NAFLD cases. Stress, eating when bored, loss of motivation and thinking in 'black and white' have been identified as the main barriers to weight loss in CBT programs (30). These cognitive factors were addressed in our program, and the development of coping strategies might have improved weight loss outcomes.

To cope with this difficulty, the effects of treatments were analyzed using a propensity score approach. The results are definitely less solid than those obtained by randomised controlled trials (31), but adjusting by propensity produces valuable data reflecting the "real world" of disease treatment and the procedure is largely accepted in chronic diseases. The propensity score was developed on the basis of individual characteristics, including factors related to barriers to group participation; comparison by propensity in the matched population provides a comparison similar to that obtained by random allocation, and further strengthens the complete series.

Effects on liver enzymes levels were largely confirmed by the sensitivity analysis having the updated healthy ranges of ALT (26) as dependent variable. Although a few studies failed to validate liver enzymes as surrogate marker of disease severity (32), other studies showed an association of elevated ALT with advanced disease (33), progression to diabetes (34) and to MS (35), and of cardiovascular risk in the general population (36), also within "healthy" ranges. In conclusion, any decrease in ALT may be beneficial, and our data suggest that CBT is likely to promote a significant advantage over prescriptive diet in NAFLD subjects.

The CBT program was associated with a larger weight loss in our NAFLD cases. The 7% decrease in BODY WEIGHT was selected as outcome measure in keeping with several intervention studies of CBT in metabolic disorders (14, 19), including the very recent trial comparing CBT with standard nutritional treatment in NASH (18). In this last study a weight loss > 7% was indeed associated both with improved biochemistry and with improved liver histology. Interestingly, the effectiveness of weight loss on histological outcomes was partly independent of treatment allocation, but the weight loss target was more frequently reached in CBT-treated subjects. However, RCT studies in the area of behavioral modifications are hampered by a very high attrition rate; in spite of local advertisement, intense support and honorarium at completion of trial, this study recruited only 65 cases, 41 entered the study and only 28 completed the study (18).

Reduced levels of alanine aminotransferases were not solely related to decreased body weight, since the results were partly maintained after adjustment for differences in weight loss. The CBT program devoted part of its education to implement physical activity in NAFLD patients. The program was largely derived from a CBT program for the treatment of obesity, coupled with a program specifically devoted to physical activity used to reinforce weight loss and weight loss maintenance (37). NAFLD patients are characterized by low levels of physical activity (38), and higher levels of exercise are associated with greater reduction in ALT, independent of weight change (39). Four weeks of aerobic exercise training was shown to be adequate to reduce hepatic triglyceride by 21% in the absence of body weight loss (40). In order to achieve and maintain behavior changes associated with greater physical activity, specific cognitive abilities must be implemented. This was part of the CBT program, and translated into an increase in physical fitness in the subpopulation where it was tested at 6-month follow-up. Improved physical fitness has been previously associated with decreased liver fat (41), and may account for the relative independence of enzyme changes from weight loss in the CBT group. Potential strategies to improve uptake of exercise in NAFLD have been recently reported, and should be incorporated into the standard of care of Liver units (42).

In addition to reduced liver enzymes, CBT improved insulin sensitivity in the long-term. After 2 years, the CBT program was associated with an increased probability to achieve normal HOMA-R, after adjustment for propensity. The statistical modeling suggested that the amount of weight loss has a pivotal effect on this outcome, as well as on liver enzymes. In the Diabetes Prevention Program, CBT was extremely effective in reducing the progression to

MS in subjects at risk of diabetes (43). In our cases, with a high prevalence of obesity class 2 or more or overt diabetes, the effects were mostly limited to triglyceride and HDL-cholesterol levels, or to reduced blood pressure. However, also treatment with oral hypoglycemic agents was reduced or stopped during follow-up, in keeping with improved insulin sensitivity.

The study has limitations too. A major limitation is the lack of histological data. The use of liver biopsy for diagnostic and outcome purposes in NAFLD is a matter of discussion outside research projects (44), because it is costly, rarely impacts on treatment decisions and is potentially dangerous. The present analysis is based on the standard of care provided to our patients, where NAFLD is tentatively diagnosed by biochemistry and liver ultrasonography. However, in over 90% of cases the diagnosis was also in keeping with a recently validated predictive algorithm (24), without quantitative differences in liver fat between groups. According to our protocol, liver biopsy is postponed and only proposed to patients who fail to improve with standard treatment. Recently, new tests of fibrosis have been validated (45), but were not available when the study was planned. Future studies should expand the limited experience of CBT against histological outcomes reported so far (18), or test the effectiveness of lifestyle modifications against validated biochemical tests of fibrosis.

Second, the intensity and the number of contacts between patients and therapists were much higher in the CBT program than in the control treatment. In addition, the CBT program was delivered as group sessions, while participants in the control group had only individual contacts with the therapists. Therefore, the more favorable results obtained by the CBT program on weight loss, liver enzymes, and other metabolic indices might also be the consequences of the more intense and frequent contacts with the therapists or of the group support. Future studies should clarify this important issue.

It is also possible that patients accepting the CBT program form a rather selected group with potentially higher intrinsic motivation, related to higher BMI and multiple comorbidities (46), as well as the higher prevalence of females, who generally have more time available for intensive group care and different motivation for weight loss (47). These factors are expected to translate into better weight loss outcomes. In the future, a quantitative assessment of motivation should be introduced as a possible baseline indicator of treatment allocation and adherence.

In conclusion, data derived from our observational analysis support CBT as a useful approach to NAFLD treatment, to replace the standard dietary approach. Any effort should be done to

provide motivated patients effective treatment, as well as remove barriers that may reduce their compliance. Both patients and physicians should consider lifestyle changes as an essential component of treatment to be systematically offered to NAFLD cases, not merely as an optional adjunct to drug treatment.

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Legend for figures

Figure 1

Prevalence of features of the ATPIII-defined metabolic syndrome in the NAFLD population, divided according to the type of treatment program (open bars, Prescriptive Diet; closed bars, Cognitive-Behavioral Treatment).

Note that the only difference is in the prevalence of cases with waist circumference ≥102 cm in males and ≥88 cm in females ($p < 0.001$).

Figure 2

Effects of different treatment programs on percent weight loss (upper panel), HOMA values (middle panel) and alanine transaminases (lower panel).

Closed circles identify CBT treatment; open circles are subjects treated by the prescriptive diet. Data are presented as means ± 95% confidence intervals. The time courses of the three variables are significantly different between groups (repeated measures, time x treatment ANOVA)

Table 1

Clinical characteristics of subjects treated by the cognitive-behavioral program and by prescriptive diet (mean ± SD or percent of cases *(95% confidence interval)).

	CBT group (n = 68)	Prescriptive diet (n = 82)	P value
Female gender (%)	64 (49 – 74)*	35 (25 – 49)*	< 0.001
Marital status (Single/Married/Widowed or Divorced)(%)	22/69/9	41/50/9	0.035
Education (Primary/Secondary/ Vocational/Degree)(%)	12/38/34/18	10/33/40/17	0.869
Profession (Student/Housewife/ Employee/Self-employed/Retired)(%)	4/11/49/13/23	6/0/61/11/22	0.053
Place of residence (within town/ metropolitan area/regional area) (%)	62/29/9	63/26/11	0.825
Age (years)	53 ± 12	50 ± 14	0.159
Body mass index (kg/m^2)	36.2 ± 4.7	30.5 ± 5.1	< 0.001
Waist circumference (cm)	110 ± 11	106 ± 12	< 0.001
NGT/IFG-IGT/Diabetes° (%)	48/21/31	50/23/27	0.825
Fasting glucose	105 ± 24	107 ± 29	0.802
Fasting insulin (µU/mL)	21.0 ± 8.7	16.8 ± 8.6	0.002
HOMA (%)	5.53 ± 2.68	4.45 ± 2.52	0.012
HDL-cholesterol (mg/dL)	48.0 ± 10.3	46.4 ± 12.8	0.377
Triglycerides (mg/dL)	178 ± 77	205 ± 108	0.100
Systolic pressure (mmHg)	134 ± 13	132 ± 13	0.206
Diastolic pressure (mmHg)	85 ± 8	85 ± 9	0.933
Aspartate aminotransferases (U/L)	38 ± 17	43 ± 22	0.167
Alanine aminostransferases (U/L)	64 ± 33	73 ± 42	0.165
Prevalence of criteria of the metabolic syndrome (0/1/2/3/4/5)(%)	2/7/21/26/35/9	4/15/16/30/28/7	0.578

°NGT, normal glucose tolerance; IFG, Impaired fasting glucose; IGT, impaired glucose tolerance

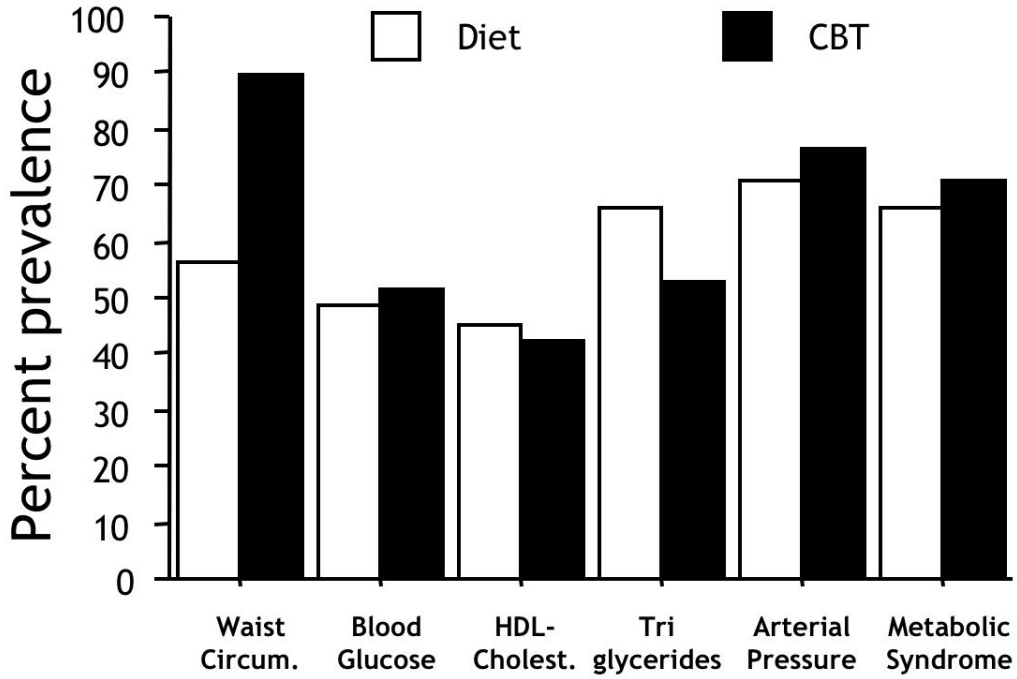
Table 2

Logistic regression models on the association of treatment program with weight changes (> 7% initial body weight), normal ALT levels, normal HOMA-IR and reduced score of the metabolic syndrome at 6 months and at 2 years in NAFLD subjects.

	6-month results OR (95% CI)	2-year results OR (95% CI)*
Dependent variable: weight loss > 7% initial b.w.		
Comparator (Prescriptive diet)	1	1
CBT program (unadjusted)	4.15 (1.76 - 9.75)	3.18 (1.44 - 7.00)
Adjusted for propensity	2.22 (0.86 - 5.75)	2.53 (1.04 - 6.14)
Dependent variable: normal ALT (<40 mU/mL)		
Comparator (Prescriptive diet)	1	1
CBT program (unadjusted)	3.46 (1.76 - 6.81)	4.09 (2.06 - 8.12)
Adjusted for propensity	3.26 (1.51 - 7.05)	4.13 (1.88 - 9.08)
Adjusted for propensity and % change in b.w.	2.58 (1.18 - 5.72)	3.57 (1.59 - 8.00)
Dependent variable: normal HOMA-IR (<2.7%)		
Comparator (Prescriptive diet)	1	1
CBT program (unadjusted)	2.53 (0.95 - 6.76)	4.79 (1.89 - 12.13)
Adjusted for propensity	2.41 (0.79 - 7.35)	7.15 (2.39 - 21.36)
Adjusted for propensity and % change in b.w.	2.32 (0.78 - 7.24)	5.21 (1.74 - 15.59)
Dependent variable: decreased score of the Metabolic Syndrome		
Comparator (Prescriptive diet)	1	1
CBT program (unadjusted)	0.95 (0.49 - 1.84)	2.16 (1.11 - 4.19)
Adjusted for propensity	1.51 (0.33 - 6.96)	2.69 (1.23 - 5.86)
Adjusted for propensity and % change in body weight	1.05 (0.51 - 2.26)	1.97 (0.87 - 4.45)

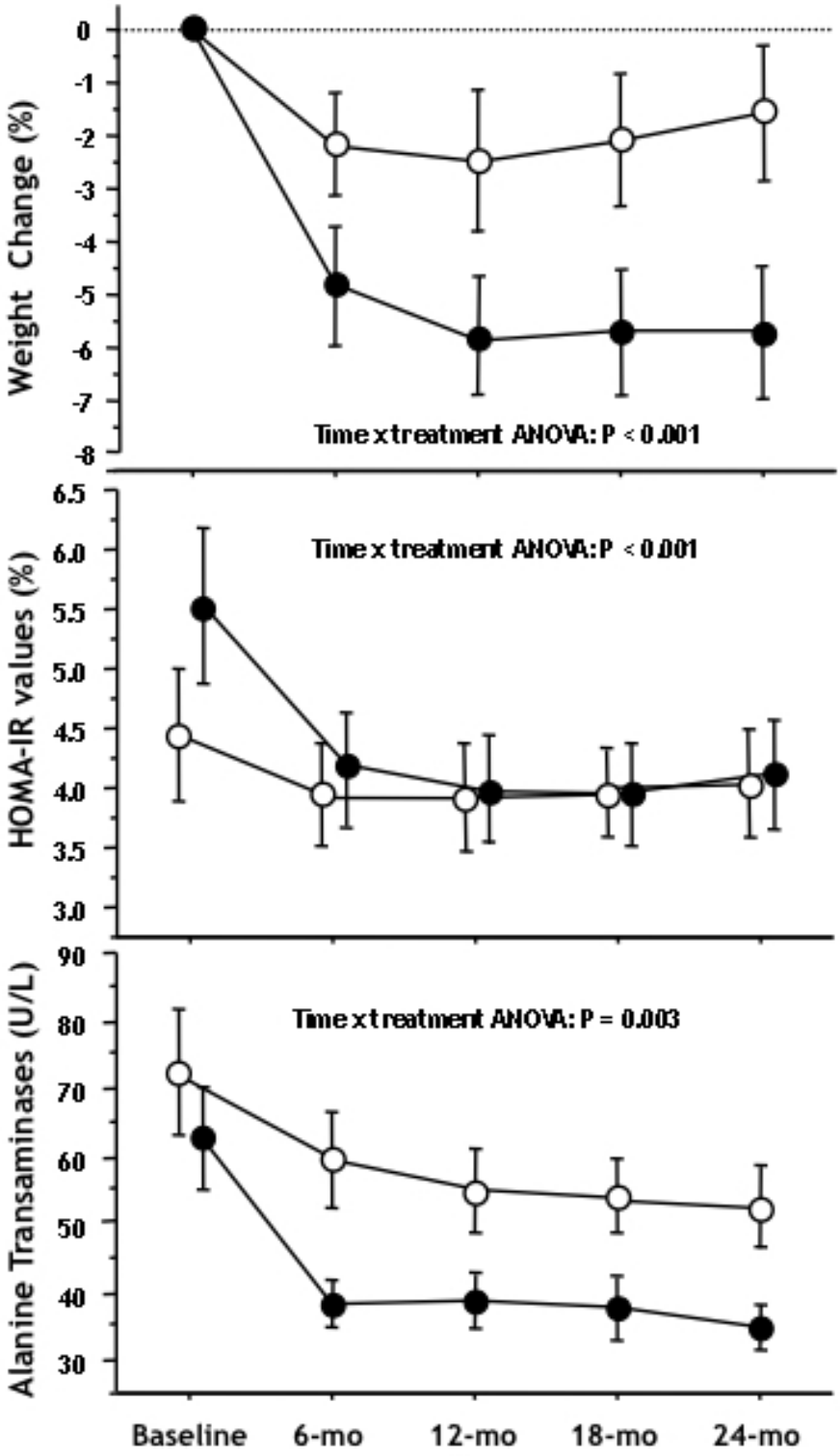
*Two-year data were analyzed by intention-to-treat using the last-observation-carried-forward technique (cases missed at follow-up: Diet 3, CBT, 4).

Figure 1



Prevalence of features of the ATPIII-defined metabolic syndrome in the NAFLD population, divided according to the type of treatment program (open bars, Prescriptive Diet; closed bars, Cognitive-Behavioral Treatment).

Figure 2



Effects of different treatment programs on percent weight loss (upper panel), HOMA values (middle panel) and alanine transaminases (lower panel).
Closed circles identify CBT treatment; open circles are subjects treated by the prescriptive diet. Data are presented as means ± 95% confidence intervals. The time courses of the three variables are significantly different between groups (repeated measures, time x treatment ANOVA)