ORIGINAL PAPER

DOI: http://dx.doi.org/10.15403/jgld-3758

The Role of Psychotherapy in the Treatment of Patients with Non–alcoholic Fatty Liver Disease and Obstructive Sleep Apnea

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ABSTRACT

Background & Aims: Non-alcoholic fatty liver disease (NAFLD) is a metabolic disease with extensive multi-organ involvement, whose extra-hepatic manifestations include diabetes mellitus type 2, cardiovascular disease, obstructive sleep apnea (OSA), chronic kidney disease, and polycystic ovary syndrome. Our hypothesis was that there was a strong psychological component in NAFLD and OSA suffering patients and that psychotherapy would be helpful in the treatment of the mentioned diseases.
Methods: Of 144 initially selected patients (with NAFLD, obesity and OSA), 32 patients agreed to undergo psychotherapy, and 31 therapy-naive NAFLD and OSA patients agreed to participate as controls.
Results: Psychological evaluation revealed that self-esteem rose significantly after one-year psychotherapy (p=0.005). Body mass index (BMI) was significantly lower after psychotherapy, followed by the changes in laboratory results. Binomial logistic regression revealed that the reduction of BMI in high probability led to self-esteem improvement (p=0.03).
Conclusions: Psychotherapy was an efficient supporting method in the treatment of patients with NAFLD, obesity and OSA. It raised self-esteem and stimulated the motivation for further treatment of obesity, as one of the important factors for NAFLD and OSA. Still, it is advisable to use psychotherapy in combination with other clinical methods of treatment.

Key words: non-alcoholic fatty liver disease – sleep apnea – obesity – body mass index – psychotherapy.

Abbreviations: AHI: apnea-hypopnea index; BMI: body mass index; CBP: cognitive behavior psychotherapy; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MRI: magnetic resonance imaging; NAFLD: non-alcoholic fatty liver disease; ODI: oxygen desaturation index; OSA: obstructive sleep apnea; PSG: polysomnography; SpO2: oxygen saturation; T2DM: diabetes mellitus type 2.

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Received: 27.02.2021
Accepted: 16.07.2021

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has been recognized as a growing global public health problem, affecting 6-45% of the general population, rising up to 70% in patients with type 2 diabetes mellitus or 90% in morbidly obese patients [1]. NAFLD is the most frequent cause of liver disease in the Western world and among the leading causes of liver cirrhosis [1], hepatocellular carcinoma [2] and liver transplantation [3]. Obesity, on the other side, is a disease with an established association with the incidence of NAFLD, but also its severity [4-5]. Considered to be the problem of Western countries, obesity and NAFLD, in the past two decades, following urbanization in many Asian countries, has also led to a sedentary lifestyle and over nutrition, setting the stage for the epidemic of obesity [6]. Apparently, obesity is becoming a worldwide problem that causes not only medical consequences but also disturbances in psychosocial functioning. Being obese today is a great burden since contemporary societies stigmatize such persons thus making them psychologically very uncertain about their physical appearance [7]. Recent studies have demonstrated that obstructive sleep apnea (OSA) is associated with the development and evolution of NAFLD, independent or associated with obesity or other shared risk factors [8]. Obstructive sleep apnea refers to chronic intermittent hypoxia that induces the narrowing of the upper airways during sleep producing sleep fragmentation which leads to a

decreasing quality of life [9]. This condition may lead to the development and aggravation of NAFLD [10]. Investigating connection between NAFLD and OSA is often found to be very challenging due to its relevance to coexisting cardiovascular and metabolic diseases and disorders [11].

Higher rates of NAFLD are shown in patients suffering from psychiatric disorders and illnesses, indicating common risk factors and pathophysiological links between these entities, with the specific metabolic syndrome at their core [12]. An increasing body of evidence confirms the role of these links as a precondition for developing psychiatric disorders [13].

Psychiatric patients suffer from a significant reduction in life expectancy, with high rates of all-cause mortality especially cardiovascular but also metabolic syndrome defined as a combination of abdominal obesity, high blood pressure, low high-density lipoprotein cholesterol, elevated triglycerides, and hyperglycemia [14-15]. There is a link between psychiatric disorders such as a bipolar disorder, depressive or schizophrenia spectrum and metabolic syndrome both because of unhealthy lifestyle and medication use. Also, persistence of any psychiatric condition makes a greater incidence of developing a somatic condition [13, 16-17]. In the case of psychiatric treatment of the patients with NAFLD and OSA, integrative approach, which refers to both psychotherapy and pharmacotherapy, showed good results. This includes psychotherapy as a possible core of the treatment; different psychotherapy modalities showed positive improvement in one's general condition. Previously conducted investigations showed that psychotherapy methods were a significantly valuable help to the conventional medical treatment, and that there were no differences in the outcome regarding the technique used. There are many modalities of psychotherapy such as cognitive behavioral therapy, hypnotherapy, and it is advised that a specific modality of psychotherapy should be used that suits the best both an experienced therapist and the personality and condition of a patient [18].

The obvious association between obesity and NAFLD, led us to an idea to involve psychotherapists in the therapy of patients with NAFLD and OSA. We hypothesized that psychotherapy directed at obesity reduction could improve the general health state of patients with NAFLD and OSA.

METHODS

This study involved a group of first-diagnosed, therapy-naive NAFLD patients, out of which 144 (96 males and 48 females), aged 34-57 (mean 47.88 ± 6.07), satisfied the recruiting criteria for the study and control groups. The grouping criterion for the division into the study and control groups was the presence of obstructive sleep apnea (OSA), body mass index (BMI) higher than 30 and the acceptance of psychotherapeutic treatment. Body weight and height were measured in bare feet and light clothing in the morning with the same equipment. Body mass index was calculated by dividing body weight by squared height (kg/m^2) (Fig. 1).

The study was approved by the Ethical Committee of the Dr Dragisa Misovic–Dedinje Clinical and Hospital Center, Belgrade (approval number 18-6685/2019).

Recruiting criteria were: 1) NAFLD patients older than 18; 2) no previous history of viral hepatitis of any kind, haemochromatosis, autoimmune hepatitis, cirrhosis or other chronic liver diseases 3) patients who did not previously use specific NAFLD therapy nor were on a diet /indulged in any intense physical activity; 4) no presence of severe cardiopulmonary disease; 5) presence of OSA syndrome assessed by polysomnography; 6) the absence of endocrinological disorders: hypothyroidism, hypercorticism, polycystic ovary syndrome; 7) no history or clinical signs of excessive alcohol abuse (>20 g/day for males and >10 g/day for females); 8) no psychiatric disease and/or psychiatric medication history or any other hepatotoxic drugs; 9) no visible

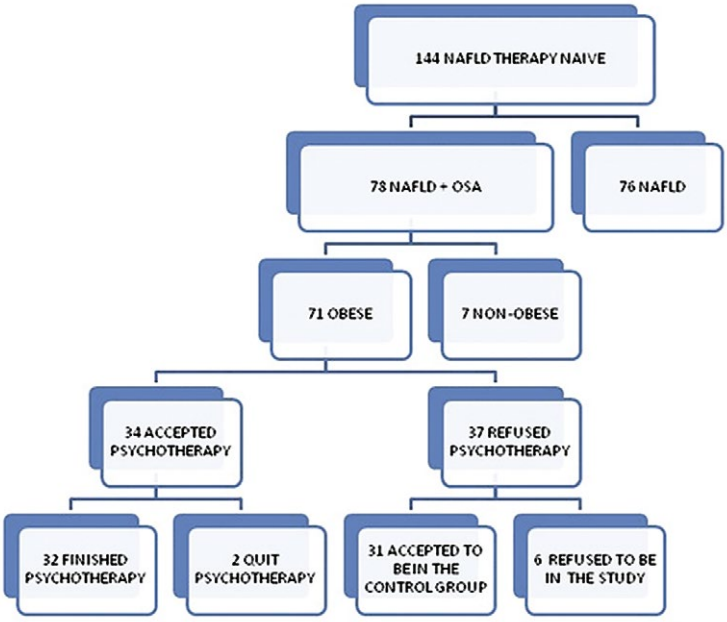

Fig. 1. Patient selection flow-chart

traces of the illicit drugs abuse (negative urine multiple drug test on 10 kinds of drugs: cannabinoids, opiates, amphetamines, 3,4-methylenedioxymethamphetamine, cocaine/crack, benzodiazepines, tricyclic antidepressants, barbiturates, methadone, buprenorphine); 10) no visible focal or diffuse changes in the gray matter of the brain on magnetic resonance imaging (MRI); 11) Fazekas score 0 on MRI scan (Fazekas score is the estimated level of the white matter vascular changes, and is the aftermath of brain vessels atherosclerotic changes); 12) absence of any rheumatological disease; 13) patients who used antidiabetic drugs, insulin, antilipemic drugs, uricosuric drugs, steroids and oral contraceptives were omitted from the study; 14) BMI equal or higher than 30 kg/m^2.

Laboratory Analyses

Fasting blood was taken in the morning for the measurement of serum glucose, and lipid profile comprising total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, aminotransferases and gamma-glutamyl transpeptidase All the tests were run by AO-BK-200 mini Auto Biochemistry Analyzer, Alpha Omega Electronics, Madrid, Spain.

Ultrasonography

The diagnosis of NAFLD was performed by ultrasonography; additionally transient elastography (FibroScan) quantified the fibrosis. The liver was assessed as normal when the consistency was homogeneous, displayed fine level echoes, minimally hyperechoic or even isoechoic in contrast to the regular renal cortex. Mild steatosis was evaluated as a minor increase in liver echogenicity. In moderate steatosis, there were visual images associated with intrahepatic vessels, the slightly damaged diaphragm and the existence of increased liver organ echogenicity. Severe steatosis was evaluated as a marked increase in hepatic echogenicity, poor penetration of posterior segment from the right lobe of the liver, poor or no visual images from the hepatic vessels and the diaphragm [19]. FibroScan ® (Echosens group) was used to quantify the fibrosis in the liver parenchyma. For NASH/NAFLD the fibrosis was quantified as follows: F0-F1 no or mild fibrosis (2 – 7 kPa), F2 moderate fibrosis (7-10 kPa), F3 severe fibrosis (10 – 14 kPa), F4 advanced fibrosis or cirrhosis (higher than 14 kPa).

Polysomnography

Sleep staging was scored according to the criteria of the American Academy of Sleep Medicine [13]. Apnea was defined as decrements in airflow ≥90 % from baseline for ≥10 s. Hypopnea was defined as a 30% or greater decrease in flow lasting ≥10 s and was associated with a 4% or greater oxyhemoglobin desaturation. The number of apneas and hypopneas per hour of sleep was calculated to obtain the apnea-hypopnea index (AHI). The oxygen desaturation index (ODI) was defined as the number of dips in oxygen saturation (SpO2) ≥4% per hour of total sleep time. OSA was defined as normal: AHI<5, mild sleep apnea: 5≤AHI<15, moderate sleep apnea: 15≤AHI<30 and severe sleep apnea: AHI≥30 events/h [20].

The participants underwent polysomnography (PSG) in the sleep department. It was performed within four weeks of MRI scan and neuropsychological testing. Nocturnal PSGs were collected on ambulatory recording system with the Alice PDx portable diagnostic recording device (Philips Respironics), together with nasal airflow which was recorded with the nasal pressure transducer. Respiratory effort was assessed using thoracic and abdominal bands; blood oxygen saturation was revealed by pulse oximetry. Patients were advised not to disturb usual bed-time week rhythm and were required to abstain from caffeinated beverages (coffee, caffeinated soda) at least eight hours before, and especially during PSG data collection. The study was reported by an accredited sleep physician.

Psychotherapy

Before the initial individual session, all patients fulfilled the 25-item Obesity Questionnaire, Serbian version. All patients went to individual sessions, during which an estimation of the damage that past trauma events had made was done through specific psychotherapy module. Cognitive behavior psychotherapy (CBT) module was used to modify and decrease both psychological and somatic manifestations of depression and anxiety such as insomnia and sleep apnea. Due to OSA, cognitive functions may be seriously disrupted and impaired and compensation for the possible defects can be done by using the CBT which is based on cognitive principles. The therapy lasted one year, one time per week. Two patients left the therapy after six weeks, claiming that it was not efficient.

Psychological Testing

Before and after psychotherapy the patients were offered to fill in Hamilton's depression rating questionnaire. Only the first 17 items were scored: equal or lower than 7 corresponded to no depression, 8-13 to mild depression, 14 – 18 to moderate depression, 19-22 to severe depression, equal or higher than 23 very severe. Testing was provided by psychiatrists.

The patients underwent the Rosenberg Self Esteem test [21], Serbian version, before and after the therapy. This test is routinely used. Rosenberg's test is a 10- item test used to evaluate self-esteem level. The patients themselves filled in the test. The maximum score is 30 points. Scores between 15 and 25 are within normal range. Scores below 15 suggest low self-esteem.

Statistics

Statistical testing was performed by the commercially available software (SPSS 17.0, Inc, Chicago Il, US). Besides measures of central tendency [mean and standard deviation (SD), minimum and maximum)], potential differences in mean values were assessed with the Student's t test for independent samples for parametric and chi square test for non-parametric data. Correlation was tested with the Spearman and Pearson's correlation test. Possible dependence between the non-parametric parameters was estimated by binomial logistic regression. All the testing was performed on the 95% probability level.

All the participants were well acquainted with the details of the study aim and design before entering the program. They all subsequently signed a written consent.

RESULTS

The demographic data are shown in Table I.

Table I. Patients' demographic data

Intervention group	Intervention group N =32	Control group N = 31	Total N=63	p
Parameter				
Age (years ± SD)	46.39±9.92	47.62±6.97	46.94±9.00	0.677
Gender (male), N (%)	29 (90.6)	28 (90.3)	57 (90.5)	0.150
Education level				
Secondary school	6 (18.7)	8 (25.8)	14 (22.2)	0.170
High school	14 (43.7)	13 (41.9)	27 (42.9)	
University	12 (37.6)	10 (32.3)	22 (34.9)	

Psychological evaluation revealed that self-esteem rose significantly after one-year psychotherapy (Table II). Inversely, the Hamilton depression index did not significantly change after psychotherapy, despite the fact that severity of depression decreased. The same trend was kept in the control group which regularly continued with NAFLD and OSA therapy but did not undergo psychotherapy.

Body mass index was significantly lower in the intervention group after psychotherapy, followed by the changes in cholesterol, HDL, LDL, triglycerides, aspartate transferase, alanine transferase and gamma - glutamyl transpeptidase which improved (Table III). Binomial logistic regression revealed that the reduction of BMI in high probability led to self-esteem improvement: OR=8.4, 95%CI:1.19-58.5, p=0.03.

The values of OSA indexes are presented in Table IV. The distribution of the cases based on AHI and ODI values differed among the intervention group before and after psychotherapy, while the intervention group and control group differed in a number of severe OSA cases only before psychotherapy. Afterward, there was no difference in the distribution.

The grades of steatosis and liver fibrosis are shown in Table V. Significant reduction of the level of fatty liver after psychotherapy was noticed only in the group of patients with moderate steatosis whereas there was no statistically significant difference in the degree of fibrosis before and after psychotherapy in the observed groups (Table V).

DISCUSSION

In obese patients with NAFLD and OSA the most conjoined psychiatric conditions are anxiety, somatoform, mood disorders as well as personality disorders [22]. In psychiatry, two major therapeutic approaches in treatment are recognized, psychotherapy and pharmacological treatment. The fact is, that neither the psychotherapy nor pharmacology solitary approach works best. Particular modalities in psychotherapy have been used as approaches to specific functional gastrointestinal disorders. There are many modalities of psychotherapy and CBT and the most suitable should provide patients' cognitions about their problems and ways to control them by learning new, modified approaches to behave (through experience).

Searching for the predictors of psychotherapy and weight loss outcome, Sasdelli et al. [23] revealed that weight loss target at 6 months was predicted by the lower levels of anxiety in females, not in males (STAI-Y1: OR=0.98, 95%CI: 0.97–0.99; STAI-Y2: OR=0.99, 95%CI: 0.97-1.00). Body appearance was a negative predictor for 6-month success (OR=1.95, 95%CI: 1.21–3.15), whereas concern for present health was associated with 10% weight loss at 24 months (OR=1.66; 95%CI: 1.04–2.65). Results for the level of depression related to the Hamilton scores did not show much improvement after psychotherapy sessions which is in correlation with the previous studies.

Our results are in accordance to Karasu et al. [24], that psychotherapy was useful in assisting with conflicts regarding

Table II. Depression and self-esteem frequencies.

Parameter	Before psychotherapy		After psychotherapy			Comparison of parameters in interventional group (before and after CBT)
	Intervention group	Control group	Intervention group	Control group	p	p
Hamilton depression rating scale, N (%)						
No depression	3 (9.4)	2 (6.4)	6 (18.8)	4 (12.9)		
Mild	11 (34.4)	9 (29.1)	16 (50)	15 (48.4)	0.43	0.18
Moderate	15 (46.8)	18 (58.1)	9 (28.1)	11 (35.5)		
Severe	3 (9.4)	2 (6.4)	1 (3.1)	1 (3.2)		
Rosenberg Self Esteem, N (%)						
Low	24 (75)	15 (48.4)	5 (15.6)	15 (48.4)	<0.0001	0.03
Adequate	8 (25)	16 (51.6)	27 (84.4)	16 (51.6)		0.005

CBT: cognitive behavior psychotherapy.

Table III. Body mass index and laboratory parameters

Index	Before psychotherapy		After psychotherapy		Significance (p)	
	Intervention group	Control group	Intervention group	Control group	Before	After
					Intervention group	Intervention group - control group
Body mass index (BMI, kg/m^2)	33.6 ± 8.3	32.7 ± 8.2	25.8 ± 5.5	29.7 ± 5.8	<0.0001	<0.01
Cholesterol (mmol/l, mean ± SD)	5.2 ± 0.7	5.3 ± 1.1	4.4 ± 1.0	4.7 ± 1.1	<0.001	0.298
HDL (mmol/l, mean ± SE)	0.9 ± 0.1	0.9 ± 0.1	1.4 ± 0.02	1.37 ± 0.07	<0.05	0.365
LDL (mmol/l, mean ± SE)	0.10 ± 0.1	0.16 ± 0.1	1. 6 ± 0.1	1.2 ± 0.1	<0.001	0.02
Triglycerides (mmol/l, mean ± SE)	2.8 ± 0.3	2.7 ± 0.4	1.6 ± 0.2	1.8 ± 0.1	<0.001	0.03
Aspartate aminotransferase (IU/L, mean ± SE)	80.0 ± 12.3	65.0 ± 9.8	45.0 ± 7.6	50.0 ± 6.2	<0.0001	<0.01
Alanine aminotransferase (IU/L, mean ± SE)	73.0 ± 11.8	56.0 ± 6.5	49.0 ± 7.9	47.0 ± 6.7	<0.0001	<0.01
Gamma-glutamyl transpeptidasa (IU/L, mean ± SE)	98.0 ± 13.0	77.0 ± 10.9	57.0 ± 6.3	65.0 ± 9.1	<0.001	0.01

HDL: high density cholesterol; LDL: low density cholesterol.

excessive weight, body image, relationship to food and disordered patterns of eating, and dealing with the prejudice and overt discrimination obese patients may experience.

Recent studies dealt with laboratory parameters as the indicators of obesity, NAFLD and OSA [25–28]. Bhatt et al. [25] suggested that OSA and NAFLD operated as independent contributors to the increased systemic inflammation that occurs in overweight/obese subjects. Results of Musso et al. [29] implied that OSA contributed to the obesity, hypertension, diabetes mellitus type II (T2DM), and cardiovascular diseases. Its relationship with NAFLD is poorly researched, and it is also debated whether OSA promotes liver injury independently of coexisting comorbidities, including obesity, insulin resistance, and metabolic syndrome. In obese subjects, a study indicated that chronic intermittent hypoxia increased liver injury and inflammation, but the relationship between OSA to NAFLD was controversial [30]. Authors are almost unanimous about the necessity of obesity treatment in NAFLD patients. Canfora et al. [31] suggested the gut microbiota regulation by products derived from microbial carbohydrate and protein fermentation, emphasizing therapeutic role in relation to obesity and obesity-associated insulin resistance, T2DM and NAFLD, and discussed the mechanisms involved.

Some authors recommend pharmacological therapy for obesity [32]. Anti-obesity drugs investigated in NAFLD were orlistat, glucagon-like peptide-1 analogs; some other drugs were not approved (e.g., lorcaserin, phentermine hydrochloric, phentermine/topiramate and naltrexone/bupropion) and some were not investigated (e.g., sodium-glucose cotransporter-2 inhibitors, farnesoid X receptor ligands). If the combination of lifestyle modification and pharmacotherapy also fails, then bariatric surgery should be considered in selected morbidly obese individuals [33]. Bariatric surgery was also suggested by Schiavo et al. [34]. During the preparation for bariatric surgery,

Table IV. Apnea-Hypopnea Index (AHI) and Oxygen Desaturation Index (ODI) before and after psychotherapy

Parameter	Before psychotherapy			After psychotherapy			Comparison of parameters in interventional group (before and after CBT)
	Intervention group	Control group	p	Intervention group	Control group	p	p
Apnea-Hypopnea Index, N (%)							
No OSA (<5)	5 (15.6)	4 (12.9)	0.03	6 (18.8)	4 (12.9)	0.77	0.63
Mild (5-15)	3 (9.4)	6 (19.4)		11 (37.4)	5 (16.1)		
Moderate (15- 30)	15 (46.9)	18 (58.1)		13 (40.6)	20 (6.5)		
Severe (>30)	9 (28.1)	3 (9.6)		2 (6.2)	2 (6.5)		
Oxygen Desaturation Index, N (%)							
No OSA (<5)	3 (9.4)	4 (12.9)	0.005	4 (12.4)	5 (16.1)	0.03	0.22
Mild (5-14)	5 (15.6)	6 (19.4)		14 (43.8)	8 (25.8)		
Moderate (15- 29)	12 (37.5)	19 (61.3)		14 (43.8)	16 (51.6)		
Severe (>30)	12 (37.5)	2 (6.4)		0	2 (6.5)		

CBT: cognitive behavior psychotherapy; OSA: obstructive sleep apnea.

Table V. Grade of liver steatosis and degree of liver fibrosis

Parameter	Before psychotherapy			After psychotherapy			Comparison of parameters in interventional group (before and after CBT)
	Intervention group	Control group	p	Intervention group	Control group	p	p
Steatosis (ultrasonography evaluation), N (%)							
Mild	6 (18.8)	8 (25.8)	0.532	13 (40.6)	6 (19.3)	0.254	0.132
Moderate	18 (56.2)	16 (51.6)	0.452	10 (31.3)	19 (61.4)	0.114	0.06
Severe	8 (25)	7 (22.6)	0.06	9 (28.1)	6 (19.3)	0.315	0.07
Fibrosis (Fibroscan assessment), N (%)							
Mild fibrosis (2-7 kPa)	18 (56.2)	15 (48.4)	0.08	16 (50)	17 (54.8)	0.256	0.167
Moderate fibrosis (7-10 kPa)	7 (21.9)	7 (22.6)	0.296	8 (25)	7 (22.6)	0.134	0.543
Severe fibrosis (10-14 kPa)	4 (12.5)	5 (16.1)	0.08	4 (12.5)	4 (12.9)	0.314	0.153
Advanced fibrosis/cirrhosis (>14 kPa)	3 (9.4)	4 (12.9)	0.387	4 (12.5)	3 (9.7)	0.134	0.480

CBT was effective in reducing disordered eating behavior and depression in bariatric patients [35-36]. Most studies conducted so far lack long-term follow-up and important outcome variables (e.g., only weight loss and no psychological variables or vice versa) and had small sample sizes [36]. Nevertheless, most of the studies available reported positive changes in eating behavior outcomes after psychotherapy. Improvements in binge eating behavior were seen in the studies that employed combined mindfulness and CBT, mindful eating programs, acceptance-based practices and combination of mindfulness exercises [37-42].

Few 12 months follow-up studies, such as ours, showed improvement with a substantial reduction in BMI, general psychopathology, binge eating, and body image dissatisfaction observed in both females and males. This was accompanied by reduced scores for dietary disinhibition and hunger [43, 44]. Females showed a greater reduction in binge eating than males, but no systematic gender-related differences were observed in any of the other psychosocial variables, or in the percentage of weight loss. Hierarchical regression analysis revealed that the most influential factors associated with a change in BMI at 12 months, after controlling for age, gender, and baseline BMI, were an increase in dietary restraint and a reduction in disinhibition. Logistic regression analysis showed that the probability of achieving a 5% weight loss (63.7% of cases) significantly increased for any point of increase in dietary restraint (OR= 1.15; 95% CI: 1.09-1.21) and point of decrease in disinhibition (OR=0.92; 95%CI: 0.85-0.99) [45]. According to our results, there was no significant difference between male and female subjects, although this might be a pitfall, due to a smaller number of females.

This study has certain limitations. Purposeful sampling technique was used indicating the possibility of selection bias. Uneven distribution of gender in the study population may have an impact on external generalizability. There was a rather smaller number of patients who volunteered for psychotherapy as both psychotherapy and bariatric surgery are not recognized by the public payer (social insurance), unless their BMI is over 40 kg/m^2. Another limitation of this study is the percutaneous liver biopsy procedure that the patients with NAFLD are reluctant to consent to, due to its invasiveness, risk, and possible complications.

CONCLUSIONS

Psychotherapy, especially CBT, is an efficient method in the treatment of patients with NAFLD and OSA. It raises self-esteem and stimulates the motivation for further treatment of both obesity, as one of the important factors for NAFLD and OSA, and NAFLD as obesity consequence. The BMI decrease is an important factor that influences patients' self-esteem. Further investigations should be directed towards the evaluation of different psychotherapeutic methods in NAFLD treatment, with the particular stress on obesity. Still, it is advisable to use psychotherapy in combination with other clinical methods of treatment.

Conflicts of interest: None to declare.

Authors' contribution: B.F.F. and A.S. conceived and designed the study; M.L., D.L., M.L., B.M., Suncica Kapor, Slobodan Kapor, S.Kiurski, D.A.K. collected data; S.Kiurski, M.M.H., A.S., B.F.F. analyzed data. N.F., B.F.F., A.S., O.M. drafted the manuscript. A.S., B.F.F. revised the manuscript. All the authors approved the final version of the paper.

Acknowledgements: The investigation was partially financed by the grant of the Ministry of Education, Science and Technological Development, Government of the Republic of Serbia, no. III 41020

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