Effects of Self-Conditioning Techniques (Self-Hypnosis) in Promoting Weight Loss in Patients with Severe Obesity: A Randomized Controlled Trial

Effects of self-conditioning techniques (self-hypnosis) in promoting weight loss in patients with severe obesity: a randomized controlled trial.

Simona Bo[1*], Farnaz Rahimi[2], Ilaria Goitre[1], Bice Properzi[3], Valentina Ponzo[1], Giuseppe Regaldo[4], Stefano Boschetti[2], Maurizio Fadda[2], Giovannino Ciccone[5], Giovanni Abbate Daga[6], Giulio Mengozzi[7], Andrea Evangelista[5], Antonella De Francesco[2], Sara Belcastro[1], Fabio Broglio[1]

[1]Department of Medical Sciences, University of Turin, Turin, Italy, [2] Unit of Clinical Nutrition, Città della Salute e della Scienza, Hospital of Turin, Turin, Italy [3] Unit of Internal Medicine, Città della Salute e della Scienza, Hospital of Turin, Turin, Italy [4] Obstetric Department, Hospital of Ciriè, Turin, Italy [5] Unit of Clinical Epidemiology, CPO, Città della Salute e della Scienza Hospital of Turin, Turin, Italy [6] Division of Psychiatry, Department of Neurosciences, University of Turin, Turin, Italy [7]Clinical Biochemistry Laboratory, Città della Salute e della Scienza, Hospital of Turin, Turin, Italy

***Corresponding author**: Simona Bo, Department of Medical Sciences, University of Turin, Corso Dogliotti 14, 10126 Turin, Italy; Telephone +39(0)116336036 Fax+39(0)116335401 E-mail: simona.bo@unito.it

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What is already known about this subject?

- Overeating often involves loss of control and compulsive behaviors
- Hypnosis has been suggested as an effective tool for weight reduction
- The hypnotic techniques previously employed were long, demanding, and difficult to be performed in clinical practice on a large number of patients

What does this study add?

- Self-hypnosis added to a lifestyle intervention was effective in ameliorated satiety, quality of life, and inflammation
- Individuals who used more frequently self-hypnosis lost more weight and greatly reduced their caloric intake
- Self-hypnosis was safe and the obtained results were independent of the susceptibility to hypnosis

Abstract

Objectives: The usefulness of the rapid-induction techniques of hypnosis as adjunctive weight-loss treatments is not defined. This randomized controlled trial evaluated whether self-conditioning techniques (self-hypnosis) added to lifestyle interventions were effective in determining weight-loss, changes in metabolic/inflammatory variables, and quality-of-life (QoL) improvement with respect to traditional lifestyle approaches in severe obesity.

Methods: Individuals (BMI=35-50kg/m^2) without organic/psychiatric comorbidity were randomly assigned to the intervention (*n*=60) or control arm (*n*=60). All received exercise/behavioral recommendations and individualized diets. The intervention consisted of 3 hypnosis sessions, during which self-hypnosis was taught to increase self-control before eating. Diet, exercise, satiety, QoL, anthropometric measurements, blood variables were collected/measured at enrolment and at 1-year (trial-end). *Results:* Participants reduced their caloric intake and lost weight, without significant between-group difference (-423.8kcal, -6.5kg intervention arm; -379.0kcal, -5.6kg controls). However, habitual self-hypnosis users lost more weight (-9.6kg; β=-10.2; 95%CI -14.2 -6.18; p<0.001) and greatly reduced their caloric intake (-682.5kcal; β=-643.6; -1064.0 -223.2; p=0.005) in linear regression models. At trial-end, intervention group showed lower C-reactive protein values (β=-2.55; -3.80 -1.31; p<0.001), higher satiety (β=19.2; 7.71 30.6; p=0.001) and better QoL (β=0.09; 0.02 0.16; p=0.01). *Conclusions:* In severe obesity, self-hypnosis ameliorated satiety, QoL, inflammation, and determined greater weight loss in more frequent users.

Introduction

Due to the rising epidemic of obesity, little success and high rates of relapse of its treatment, the finding of new approaches for its care has become increasingly important.

In the past, some studies have evaluated the effectiveness of hypnosis as an adjunctive therapy for weight loss (1-3). Clinical hypnosis is a procedure in which changes in sensation, perception, thought and behavior are suggested by a therapist; the hypnotic induction produces either "a distinct state of consciousness" or a normal state with heighten suggestibility according to the different theoretical conceptions of hypnosis (1,4).

Overall, hypnosis has been recognized as an effective tool for weight reduction, even if many methodological limitations of the published research (small cohorts, lack of long-term follow-up, variations in procedures, different response measurements) have been identified, making the evaluation of treatment efficacy difficult (5). Usually, traditional hypnotic techniques were combined with social, cognitive and behavioral psychological approaches. The hypnotic procedure used varied greatly among studies, ranging e.g. from a 9-weeks program, with the presentation of eating and dieting rules during the hypnotic sessions (6), a total 24-h hypnotic treatment with a therapist, and the successive utilization of audiotapes (7), to a combination of hypnotic and behavioral therapy for twelve 120-min sessions over a period of 8.5-months (8), a multifaceted program with suggestions for relaxation, self-control, self-esteem, strengthening motivation towards change (9). Most of these treatments are long, demanding, and difficult to be performed in clinical practice on a large number of patients. Moreover, during the hypnotic sessions many researchers gave suggestions targeting aversion to specific high-calorie foods, persuading that overeating is a poison, or employing other techniques of aversion (10-11), rather than purposeful messages or pleasant suggestions for heightening the awareness of self-control and healthy functioning.

Recently, techniques with a rapid-induction phase allow the patient to go into hypnosis in a few minutes. Trained individuals can repeat the experience in complete autonomy (self-hypnosis), using little time of the day.

Overeating often involves loss of control and compulsive behaviors (12), and frequently people bring with themselves the daily stress and worries during meals, thus eating in less conscious ways and consuming more calories than necessary.

We hypothesized that self-hypnosis could be applied before eating occasions or circumstances of irrational food need, as an aid to increase awareness and self-control.

Therefore, our aims were evaluating whether in patients with severe obesity self-conditioning techniques (self-hypnosis) added to traditional lifestyle approach (diet, exercise and behavioral recommendations) were effective in determining weight loss, changes in metabolic and inflammatory variables, and improvement in the quality of life, with respect to the traditional lifestyle approach.

Methods

The methods of the present trial have been previously reported (13). The trial was conducted at the Unit of Clinical Nutrition of the "Città della Salute e della Scienza" Hospital of Turin, Italy. Participants were enrolled between January 2015-June 2016.

Inclusion criteria were: BMI 35-50 kg/m^2; age 20-70 years; being able to give written informed consent and accepting hypnosis. The exclusion criteria were: current/previous mental disorders diagnosed by an expert clinician and/or use of any psychotropic drug; insulin treatment; candidates to bariatric surgery; current (or discontinued for <6-months) treatment with anti-obesity drugs; at risk of heart failure, edema, ascites (known heart diseases, chronic liver diseases, nephrotic syndrome, renal failure; untreated or uncompensated thyroid diseases). Before enrolment, in order to exclude clinically relevant psychiatric symptoms

below diagnostic thresholds, patients were submitted to the following questionnaires: the Hamilton rating scale for depression (14), the Hamilton anxiety scale (15), and the Binge Eating Scale (16). Only individuals who satisfied all the three scores (respectively <8, <17 and <17) were considered for enrolment.

This prospective, randomized controlled, open-label monocentric trial was registered at ClinicalTrials.gov (identifier NCT02978105).

Intervention

Eligible patients were randomized either to the experimental arm (self-conditioning techniques plus standard care) or the control arm (standard care, i.e. diet plus exercise plus behavioral recommendations) (**Figure 1**).

All the participants received a personalized diet by a trained dietician (energy ~1500±100kcal/day, 15-20% protein, 55-60% carbohydrates, 25-30% lipids), and the recommendation of performing at least 20-minutes/day of brisk walking, according to the Borg scale criteria (17). Verbal and written behavioral recommendations were given to all patients, i.e. recommendations about exercise inclusion in daily activities and simple tips to favor diet adherence (i.e. don't buy foods on an empty stomach, do not do anything else when eating, etc).

The participants were followed-up every 3-months (at 3,6,9, and 12-months after enrolment) by a dietician and a medical doctor, and a physical assessment, the recording of adverse events or effects, and a check of compliance to the protocol were performed. During visit intervals (at 1.5, 4.5, 10.5-months after enrollment), participants were called by phone and asked about adverse events and compliance to the intervention.

Subjects who withdrew from the study before 12-months for any reasons or those who during the trial took slimming products/drugs or employed techniques to lose weight other than those

recommended (e.g. very-low-calorie diets, or highly unbalanced diets) were considered as drop-outs.

Self-hypnosis

The experimental group received three individual sessions of hypnosis, performed by trained personnel (2 nurses, 1 medical doctor). To minimize the potential lack of fidelity, the health care providers were assigned to the sessions by a scheduled rotation among sessions to ensure a balanced intervention. Rapid-induction techniques were used, and the patient went into a hypnotic condition in a few minutes (18).

Timing of the hypnosis sessions was after 2-weeks, 6-weeks, and 15-weeks from randomization (13). The first session of the hypnotic procedure (lasting about 30-minutes) was briefly introduced, and information about medical hypnosis and its potential application as an amplification of personal resources to manage self-control were given. During this phase, the degree of susceptibility to hypnosis was evaluated by the eyeroll test of Spiegel (19). Thereafter, the rapid hypnotic induction was determined through a technique of attention focusing (fixing a point or focusing the attention on a part of one’s body) and ratification of what was happening; the following were the phases of full-body relaxation, of slow breathing, of imagining pleasant images and thoughts and creating an ideal "safe place" where the subject could take refuge. In this imaginary place, the subject could feel stronger, more determined, self-controlled, efficient, and able to sit at table aware of what he/she was about eating, refraining from gorging. The last phase was the anchor phase, during which the subject received a self-conditioning symbolic signal (i.e. joining the thumb with index or making the fist with the thumb folded inside the hand) by which he/she could rapidly fall under hypnosis in complete autonomy (self-hypnosis), also repeatedly during the day. The anchor stage was then checked and if necessary the procedure was repeated a second and/or third time by changing suggestions and/or the symbolic anchor signal. Finally, instructions

were given about self-hypnosis use before each meal or food-compulsion occasion for about 3-minutes (10-seconds to enter, 2-minutes of “safe place” thinking with muscle relaxation and mental well-being, and 30-seconds to exit).

In the subsequent two sessions (“reinforcements sessions”) lasting 20-30-minutes, participants reported difficulties, problems, barriers and benefits with self-hypnosis. The skill of going into hypnosis was checked again. The same suggestions of the first session were employed, and a new image was evoked to reinforce the skill to face difficulties (a metaphorical climb on a mountain top by overcoming natural obstacles). Finally, suggestions for overcoming the encountered barriers and problems were given.

The hypnotic sessions had a common core, but the way of hypnosis induction was individualized based on the participants’ characteristics.

Quality control

The participants’ acquired skills were checked during each session by the hypnotists by the evaluation of typical muscle changes (muscle inertia, levitation, catalepsy), characteristic physical appearance (variation of facial expression, movements of eyelids/eyeballs, swallowing, changes in respiratory rate, vasodilation), alteration of consciousness (partial detachment from reality, time warp, realistic images and conceived situations). The hypnotic condition achieved was considered satisfactory if all the above reported conditions were present at the same time.

In the case of a low hypnotizability, the participant was still encouraged to run the procedure before each meal and food compulsion attack.

Outcomes

The primary outcome was the between-arms weight change at 12-months after randomization.

Secondary outcomes were between-arms changes in waist circumference, arterial blood pressure, metabolic/inflammatory variables, satiety, well-being, and eating and exercise pattern.

Randomization

The list of randomization, stratified by age (50; >50 years), gender, and BMI (40; >40 kg/m^2) was generated by a variable-length block procedure, masked to researchers. The randomization procedure was centrally run through an online procedure (available at: http://www.epiclin.it). A unique code was assigned to each participant.

Blinding

Blinding participants and health professionals was not possible, owing to the nature of the intervention. Indeed, the personnel who performed the laboratory analyses, the anthropometric measurements, and collected questionnaire data was blinded to the arm assignment.

Safety

Adverse events and compliance with the study protocol was monitored both during each visit and between the visits (by phone calls). Participants were instructed to inform the researchers if adverse effects occurred.

Ethics

The study protocol received ethical approval from the local ethics committee. All the procedures were conducted according to the Helsinki Declaration. All patients provided their written informed consent to participate.

Measurements

At enrolment and at 12-months (trial end), all the participants were submitted to the following:

-3-day food record

-the Minnesota-Leisure-Time-Physical-Activity questionnaire (20)

-The Satiety Labeled Intensity Magnitude scale (21)

-The Satisfaction and well-being (EuroQol (EQ)-5 questionnaire [Index and Visual Analog Scale (VAS)] (22)

-anthropometric and arterial blood pressure measurements

-blood sample collections after an overnight fast to measure glucose, insulin, glycated hemoglobin (HbA1c), total and HDL-cholesterol, triglycerides, and high-sensitivity C-reactive protein (CRP).

Body weight and waist circumference were measured at 3, 6, 9-months from randomization, too.

Participants from the intervention arm were asked about the frequency of self-hypnosis use; they were divided in individuals with low (0-1), medium (2-3), or high hypnotizability (4) according to the score obtained by the eyeroll Spiegel test.

The physical activity level was calculated as the product of the duration and frequency of each activity (hours/week), weighted by an estimate of the metabolic equivalent (MET) of the activity and summed for the activities performed (20).

Body weight was measured to the nearest 0.1kg, and height to the nearest 0.1cm by a stadiometer (SECA model 711, Hamburg, Germany), with the participants wearing light clothes and no shoes. Waist circumference was determined by a plastic meter at the highest point of the iliac crest. Body composition was assessed by Dual-energy X-ray absorptiometry (DXA) (QDR-4500; Hologic, Bedford, MA, USA), using whole-body absorptiometry software.

Arterial blood pressure was measured by a mercury sphygmomanometer with appropriate cuff sizes (ERKA Perfect-Aneroid, Germany) in a sitting position after at least 10-min rest; the values reported were the mean of two measurements.

Laboratory methods have been previously published (13). Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) was calculated according to the published algorithm (23).

Statistical analyses

The sample size was calculated in relation to the primary outcome. Available data on patients with clinical characteristics similar to those enrolled were used. With an effect size=0.67 and a 2-tailed α-error=0.05, 48 patients per arm were needed to obtain a 90% power. This number was increased to 60, because of the possibility of drop-outs.

Endpoints analyses were based on the between-arms comparisons of the changes from baseline to 12-months after randomization (deltas). Linear regression models were used to compare deltas of the analyzed endpoints between-arms, adjusting for the baseline measurement and the randomization stratification variables [gender, age (50; >50 years), BMI (40; >40 kg/m^2)].

An intention-to-treat analysis was performed including all the randomized patients by multiple imputing missing 12-month variables, using the method of chained equations (24). Combined estimates were obtained from 50 imputed datasets.

For each randomization arm, mean changes from baseline for weight, BMI and waist circumference were estimated at 3, 6, 9 and 12-months using linear regression models for repeated measures. Interaction terms between-arms and the time point variables were included to estimate the specific mean change from baseline for each arm at fixed times. To account for the repeated measures on the same subject, mean changes from baseline were estimated controlling the standard errors with the Huber-White Sandwich Estimator (25).

The associations between hypnosis use frequencies (coded as dummy variables) and anthropometric/laboratory variables, and questionnaire scores were evaluated by linear regression models, adjusted for the randomization stratification variables.

Results

At 12-months, there were 16/60 (26.7%) individuals lost at follow-up from the intervention arm and 18/60 (30.0%) from the control arm. The main reasons for drop-outs are reported in Figure 1. No adverse event was recorded. During the trial, no death or hospitalization occurred.

No significant difference was evident between individuals who completed the trial and those who were lost, even if the latter tended to be younger and more frequently males (**Supplementary-Table 1**).

The clinical and laboratory characteristics at enrolment were very similar between the two randomization arms (**Table 1**).

Changes in lifestyle habits and drug use

Mean energy intakes significantly decreased in both groups at follow-up (respectively, in the intervention and control arms: 1470.6±281.1 and 1496.9±311.9kcal; $p<0.001$ for within-group difference in both groups). Mean differences were -423.8 and -379.0kcal respectively in the intervention and control arm ($p=0.84$). The composition in macronutrients did not significantly change from baseline to the trial end in both arms (data not shown).

Median (interquartile range) METs values at follow-up were 24.8 (27.2) and 30.5 (41.7) h/week in the intervention and control arms respectively, without significant difference in within and between-group analyses.

During follow-up, there were small variations in the therapy of the patients: hypoglycemic drugs were added to 2 and 1 subjects respectively from the intervention and control arms, lipid-lowering agents were added to 1 subject from both arms, antihypertensive drugs were suspended to 1 subject from the intervention arm and added to 1 control.

Changes in anthropometric and laboratory variables

Individuals from the two arms significantly reduced their weight, BMI, and waist circumference values from baseline to the trial end (**Supplementary-Table 2**). Within-group variations were significantly different as early as 3-months after randomization.

Changes in anthropometric and laboratory variables are reported in **Table 2**. Deltas (end-of the trial values – baseline values) did not differ between-arms, with the exception of delta CRP values which significantly decreased in the intervention arm.

Intention-to treat analyses confirmed the significant reduction in CRP values in the intervention arm (**Supplementary-Table 3**).

Changes in satiety, and health status

Participants from the intervention arm showed increased scores of satiety and quality of life at the trial end (Table 2), with within-group significant differences (respectively, $p=0.001$, $p<0.001$ and $p=0.002$ for satiety, EuroQoL VAS, and EuroQoL health status). In the controls, these scores did not change significantly. The associations between being in the intervention arm and the scores were confirmed by linear regression (Table 2), and by the intention-to-treat analyses (Supplementary-Table 3).

Frequency of self-hypnosis use

At the trial end, 16/44 (36.3%) declared to practice self-hypnosis regularly once/day, 7/44 (15.9%) more frequently than once/day, 9/44 (20.5%) less frequently than once/day, i.e. with a weekly frequency, but 12/44 (27.3%) rarely or never. The corresponding values of delta weight were: -9.6kg (≥once/day), -7.5kg (<once/day), and +0.2 (rarely or none).

The frequency of hypnosis use was significantly associated with changes in weight, BMI, waist circumference, and energy intake, after adjusting for age, gender, and BMI (**Supplementary-Table 4**). No significant association was evident with the other anthropometric and laboratory variables, or questionnaire scores.

The frequency of self-hypnosis declined with time. The prevalence of individuals practicing the procedure respectively ≥once/day, <once/day and rarely/none was 77.8%, 15.6%, 6.7% at 6 months and 72.7%, 15.9%, 11.4% at 9-months.

Hypnotizability

Participants in the intervention arm were divided according to the eyeroll test of Spiegel in individuals with low (43.2%), medium (52.3%), or high hypnotizability (4.5%) (19).

No difference in the hypnotizability scores was evident between individuals who completed or not the follow-up (Supplementary-Table 1). The susceptibility to hypnosis did not correlate with any outcomes, either the anthropometric and laboratory variables or the scores of the analyzed questionnaires.

Discussion

The use of self-hypnosis was associated with a significant between-group difference in the quality of life, satiety score, and CRP values, but not with changes in the anthropometric variables. In the intervention arm, however, the increased frequency of self-hypnosis use correlated with increased reduction in body weight, and energy intakes.

Changes in anthropometric variables

Literature reports that hypnosis leads to variable weight loss at 6-months with a difference ranging from 4 to 8 kg between the groups with and without hypnosis (2,6-7). Hypnosis has been reported to be successful not by itself as a treatment for obesity, but as a facilitator of a specific lifestyle intervention, by increasing the patient involvement in the therapeutic process (6). Therefore, usually hypnosis has been combined with behavioral approaches, and most of these treatments are long-lasting, complex, challenging, and, therefore, difficult to be performed routinely (6-9).

Our hypnotic approach had the advantage to be rapid and our intervention was less demanding and easier to be implemented in the clinical practice. However, we did not find any significant differences between arms in the change of anthropometric variables. Accordingly, a less-intensive hypnosis program, like ours, led to a lower difference in weight loss between groups, i.e. <1kg difference (26). Nevertheless, our participants from the intervention arm who used more frequently (≥once/day) self-hypnosis showed a much greater weight loss (with an adjusted mean difference of ~10kg), and reduction in energy intake when compared to those practicing rarely or not at all.

We should take into consideration the fact that after 12-months, only 52% of the participants practiced self-hypnosis ≥once/day, with a trend towards a progressive reduction of use with time. Indeed, the reported average use of hypnosis programs in the medium term (>6 months) was similar to ours (6).

The impact of hypnosis has been reported to increase over time, being more effective in the long-term, since it allows the establishment of a reinforcement in healthy behaviors that continues beyond the training period (1,6,27). Weight maintenance requires continued motivation and engagement; the use of a reinforcement incentive tool, such as self-hypnosis, might be a motivational successful strategy in promoting the maintenance of weight change. Accordingly, a significant weight loss compared to baseline at 18-months (27) or a weight loss of 10kg at 2-years (6) was reported by the few studies evaluating the long-term effects of hypnosis.

Changes in quality of life and satiety score

Both quality of life and satiety increased in our intervention arm. These changes were not associated with the frequency of self-hypnosis use.

Accordingly, satisfaction was reported to be greater in the hypnosis arms of the trials (6), and only the hypnotherapy aimed at reducing stress, but not the one that induced a negative

attitude towards food, was effective in determining a significant weight loss with respect to baseline (26). Differently from other studies which employed techniques inducing fear/hate towards eating and showing some foods as a body poison (10-11,27), we referred to methods of “ego strengthening” and esteem-enhancement suggestions, with the objective to reduce stress, and possibly emotional eating, by increasing awareness of self-control and conscious eating. Our results suggest that the improvement in patients' belief in their capacity of controlling events might play adjunctive benefits. Furthermore, typical hypnotic inductions closely resemble conventional relaxation training (1). Therefore, the finding of a better quality of life in those who have been subjected to hypnosis is not unexpected. Furthermore, our approach might have strengthened individual self-efficacy, whose increase correlates with weight loss, and favorably modulates eating behavior and food compulsivity (28).

Finally, even if individuals from both arms similarly reduced their energy intakes, satiety was significantly increased only in the intervention arm. This is in line with the known modulation of appetite and satiation associated-peptides and hormones levels through psycho-neuro-immuno- and psycho-neuro-endocrine mechanisms, even in the absence of substantial weight loss (5,26).

Change in CRP values

Participants from our intervention arm showed a significant reduction in CRP values, the most commonly used acute-phase reactant marker of inflammation. This finding is intriguing and suggests a complicate relationship between the mind and the body. It is well known that distress and quality of life are associated with inflammation and immunologic measures, and chronic, systemic inflammation has been proposed as one mechanism underlying psychologic and physical health problems (29-32). Higher levels of psychological distress have been associated with increased circulating values of CRP and other inflammatory variables though pathways including the sympathetic nervous system, and the hypothalamic-pituitary-adrenal

axis (32-34), and the associations between psychological distress and chronic age-related diseases and mortality might be modulated at least in part by inflammation, as well as other conditions, such as immunological factors, or dysregulated hormonal responses (35). Our results could have clinical implications, owing to the chronic sub-clinic inflammatory state of the individuals with obesity, and the predictive role of chronic inflammation towards cardiovascular diseases, frailty, disability, and mortality (36-37).

Hypnotic susceptibility

Hypnotizability was not a significant predictor of weight loss or other outcomes in our patients, in line with some studies and a recent meta-analysis (7,38-39), but differently from others showing a significant relationship between hypnotic susceptibility and weight loss outcomes (10,40-41).

Indeed, methods of evaluating the degree of susceptibility to hypnosis varied greatly, and its assessment has been criticized, since correlations between hypnotizability and treatment outcome might be indicators of expectancy effects, rather than effects of some special hypnotic process (1,5). Furthermore, other studies aimed at inducing deeper changes at the cognitive-behavioral level, with numerous long-lasting hypnosis sessions requiring a high capacity for trance; therefore, hypnotic abilities can assume greater importance (10,40). Contrariwise, our short-term sessions of self-hypnosis were aimed at obtaining a brief moment of relaxation, during which each participant could evoke the suggestion that he/she would be able to control the amount of food subsequently eaten. Therefore, it is reasonable thinking that the frequency of use of self-hypnosis was more important than the degree of susceptibility in our patients.

Finally, we have chosen a very simple measure for pretesting for hypnotizability, since other complex and time-requiring tests have been considered even counterproductive, because such

methods could take more time than the therapy, creating concern or irritation in the patient (39).

Limitations

The main limitation of this trial was the high percentage of drops-out (28%). Other hypnosis studies reported higher drop-out rates (6,27,42), and >50% of patients with obesity, above all the youngest, discontinued treatment in clinical practice (43). Furthermore, we took care of performing an accurate intention-to-treat analysis with imputation of missing values, and results did not change meaningfully.

The number of patients who completed the intervention was smaller than that originally defined to obtain an adequate sample size. However, rather than to a reduced power, the lack of statistical significance of some between-arm comparisons might be attributable to the effect size found which was smaller than that expected.

We used a very simple approach with three sessions of about 30-minutes each, the last of which was at 15-weeks after randomization. Therefore, the participants remained approximately 8-months without receiving any reinforcement session. Accordingly, we observed a decline in the use of self-hypnosis with time. We cannot exclude that a more intensive intervention could have resulted in a greater between-arms difference in the outcomes. However, our goal was to test a simple method, easily applicable to the largest possible number of individuals in the clinical practice.

Assessments of the quality of life and satiety were highly subjective, and the knowledge of the study arm might have influenced the participants' responses. However, there was biological plausibility in the associations found. Furthermore, CRP, a variable associated with overall distress and blindly measured, was found to be significantly associated with the intervention arm. Finally, we failed to assess other aspects, such as attitude towards hypnosis and sleep quality, which could represent potential confounding factors.

Conclusions

Self-hypnosis is a non-invasive intervention, free of side effects, which ameliorated satiety, quality of life and CRP values after 12-months. Both the cost-benefit balance of this procedure and further trials in larger samples should be performed, before final conclusions about its benefits could be drawn.

References

1) Kirsch I, Montgomery G, Sapirstein G. Hypnosis as an adjunct to cognitive-behavioral psychotherapy. Another meta-analysis. *J Consult Clin Psych* 1995;63;214-220.
2) Kirsch I. Hypnotic enhancement of cognitive-behavioral weight loss treatments-another meta-reanalysis. *J Consul Clin Psychol* 1996;64:517-519.
3) Pittler MH, Ernst E. Complementary therapies for reducing body weight: a systematic review. *Int J Obes 2005*;29:1030-1038.
4) Gamsa A. Hypnotic analgesia. In: Melzack R, Wall PD, eds. *Handbook of Pain Management.* London: Churchill Livingstone; 2003:521-531.
5) Entwistle PA, Webb RJ, Abayomi JC, Johnson B, Sparkes AC, Davies IG. Unconscious agendas in the etiology of refractory obesity and the role of hypnosis in their identification and resolution: a new paradigm for weight-management programs or a paradigm revisited? *Int J Clin Exp Hypn* 2014;62:330-359. doi: 10.1080/00207144.2014.901085.
6) Bolocofsky DN, Spinler D, Coulthard-Morris L. Effectiveness of hypnosis as an adjunct to behavioral weight management. *J Clin Psycol* 1985;41:35–41.
7) Cochrane G, Friesen J. Hypnotherapy in weight loss treatment. *J Consult Clin Psychol* 1986;54:489-492.

8) Gelo OGC, Zips A, Ponocny-Seliger E, Neumann K, Balugani R, Gold C. Hypnobehavioral and hypnoenergetic therapy in the treatment of obese women: a pragmatic randomized clinical trial. *Int J Clin Exp Hyp* 2014;62:260-291. doi: 10.1080/00207144.2014.901055
9) Vanderlinden J,Vandereycken W. The (limited) possibi- lities of hypnotherapy in the treatment of obesity. *Am J Clin Hypn* 1994;36:248-257.
10) Barabasz M, Spiegel D. Hypnotizability and weight loss in obese subjects. *Int J Eat Dis* 1989;8:335-341.
11) Johnson DL, Johnson WR. Perceived overqualification and psychological well-being. *Psychol Rep* 1996;79:659-668.
12) Laddu D, Dow C, Hingle M, Thomson C, Going S. A review of evidence-based strategies to treat obesity in adults. *Nutr Clin Pract* 2011;26:512-525. doi: 10.1177/0884533611418335.
13) Bo S, Rahimi F, Properzi B, et al. Effects of self-conditioning techniques in promoting weight loss in patients with severe obesity: a randomized controlled trial protocol. *Int J Clin Trials* 2017;4:20-27.
14) Hamilton M. Development of a rating scale for primary depressive illness. *Br J Social Clin Psycol* 1967;6:278-296.
15) Hamilton M. The assessment of anxiety states by rating. *Br J Med Psycol* 1959;32:50-55.
16) Gormally J, Black S, Daston S, Rarrdin D. The assessment of binge eating severity among obese persons. *Addict Behav* 1982;7:47-55.
17) Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exer* 1982;14:377-381.
18) Regaldo G. Manuale di ipnosi medica rapida. (Ed Regaldo, Turin, 2014)

19) Spiegel H. An eye-roll test for hypnotizability. *Am J Clin Hypnosis* 1972;15:25-28.
20) Taylor HL, Jacobs DR, Schucker B, Knudsen J, Leon AS, Debacker G. Questionnaire for the assessment of leisure time physical activities. *J Chronic Diseases* 1978;31:741-755.
21) Cardello AV, Schutz HG, Lesher LL, Merrill E. Development and testing of a labeled magnitude scale of perceived satiety. *Appetite* 2005;44:1-13.
22) Warkentin LM, Majumdar SR, Johnson JA, et al. Predictors of health-related quality of life in 500 severely obese patients. *Obesity* 2014;22:1367-1372. doi: 10.1002/oby.20694.
23) Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412-419.
24) Royston P. Multiple imputation of missing values: update of ice. *Stata J* 2005;5:527–536.
25) White H. A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. *Econometrica* 1980;48:817–838.
26) Vanderlinden J. Hypnotherapy in obesity. In Burrows GD, Stanley RO, Bloom PP (Eds.), International handbook of clinical hypnosis. (Wiley, Chichester, United Kingdom, 2001) pp. 221–232.
27) Stradling J, Roberts D, Wilson A, Lovelock F. Controlled trial of hypnotherapy for weight loss in patients with obstructive sleep apnoea. *Int J Obesity* 1998;28:278-281.
28) Shimpo M, Fukkoshi Y, Akamatsu R. Correlations between self-efficacy in resisting six temptations and dietary energy and macronutrient intake at each meal. *Eat Behav* 2014;15:563-566. doi: 10.1016/j.eatbeh.2014.08.012.

29) Fang CY. Reibel DK. Longacre ML, Rosenzweig S, Campbell DE, Douglas SD. Enhanced psychosocial well-being following participation in a mindfulness-based stress reduction program is associated with increased natural killer cell activity. *J Altern Complement Med* 2010;16:531-538. doi: 10.1089/acm.2009.0018.

30) Tursich M, Neufeld RWJ, Frewen PA, et al. Association of trauma exposure with proinflammatory activity: a transdiagnostic meta-analysis. *Transl Psych* 2014;4:e413. doi: 10.1038/tp.2014.56.

31) Passos IC, Vasconcelos-Moreno MP, Costa LG, et al. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. *Lancet Psych* 2015;2:1002-1012. doi: 10.1016/S2215-0366(15)00309-0.

32) Marsland AL, Walsh C, Lockwood K, John-Henderson NA. The effects of acute psychological stress on circulating and stimulated inflammatory markers: A systematic review and meta-analysis. *Brain Behav Immun* 2017;64:208-219. doi: 10.1016/j.bbi.2017.01.011.

33) Hänsel A, Hong S, Cámara RJa, von Känel R. Inflammation as a psychophysiological biomarker in chronic psychosocial stress. *Neurosci Biobehav Rev* 2010;35:115-121. doi: 10.1016/j.neubiorev.2009.12.012.

34) Johnson TV, Abbasi A, Master VA. Systematic review of the evidence of a relationship between chronic psychosocial stress and C-reactive protein. *Mol Diagn Ther* 2013;17:147-164. doi: 10.1007/s40291-013-0026-7.

35) Russ TC, Stamatakis E, Hamer M, et al. Association between psychological distress and mortality: individual participant pooled analysis of 10 prospective cohort studies. *Br Med J* 2012;345:e4933. doi: 10.1136/bmj.e4933.

519 36) Rohleder N. Stimulation of systemic low-grade inflammation by psychosocial stress.
520 *Psychosom Med* 2014;76:181-189. doi: 10.1097/PSY.0000000000000049.
521 37) Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress
522 and coronary heart disease: is interleukin-6 the link? *Atherosclerosis* 2000;148:209-
523 214.
524 38) Deyoub PL, Wilkie R. Suggestion with and without hypnotic induction in a weight
525 reduction program. *Psychol Rep* 1980;45:974.
526 39) Montgomery GH, Schnur JB, David D. The impact of hypnotic suggestibility
527 in clinical care settings. *Int J Clin Exp Hypn* 2011;59:294-309.
528 doi: 10.1080/00207144.2011.570656.
529 40) Anderson MS. Hypnotizability as a factor in the hypnotic treatment of obesity. *Int J*
530 *Clin Exp Hypn* 1985;33:150-159.
531 41) Jupp JJ, Collins J, McCabe M, Walker W. Hypnotic susceptibility and depth:
532 Predictors of outcome in a weight control therapy. *Austr J Clin Exp Hypn* 1986;14:31-
533 40.
534 42) Allison DB, Faith MS. Hypnosis as an adjunct to cognitive-behavioral psychotherapy
535 for obesity: A meta-analytic reap- praisal. *J Concult Clin Psychol* 1996;64:513-516.
536 43) Dalle Grave R, Calugi S, Molinari E, et al. Weight loss expectations in obese patients
537 and treatment attrition: an observational multicenter study. *Obes Res* 2005;13:1961-
538 1969.

Table 1. Baseline characteristics of the patients

	Intervention arm	**Control arm**	**Total**
Number	60	60	120
Age (years)	49.0±12.7	49.0±13.0	49.0±12.8
Males (%)	33.3	30.0	31.7
Actual smokers (%)	20.0	21.7	20.8
METS (h/week)	24.5 (28.1)	28.3 (38.0)	25.6 (32.6)
Height (m)	1.64±10.2	1.63±9.6	1.63±9.9
Weight (Kg)	110.7±17.1	108.6±16.7	109.6±16.9
BMI (Kg/m^2)	41.2±4.7	41.0±3.8	41.1±4.3
Waist circumference (cm)	122.0±12.5	121.0±11.5	121.5±12.0
Percent body fat	45.3±4.6	45.0± 6.1	45.1±5.4
Systolic blood pressure (mmHg)	130.2±16.1	130.8±13.6	130.5±14.8
Diastolic blood pressure (mmHg)	81.5±10.6	81.5±8.3	81.5±9.5
Dietary intakes			
Energy (kcal)	1872.6±589.2	1875.1±466.7	1873.8±529.2
Carbohydrates (% total kcal)	48.8±7.0	47.7±8.1	48.3±7.5
Sugars (% total kcal)	12.1±3.9	11.3±5.1	11.7±4.5
Proteins (% total kcal)	16.6±2.7	16.5±3.0	16.5±2.9
Total fats (% total kcal)	33.5±5.4	34.7±7.0	34.1±6.3
Saturated fatty acids (% total kcal)	9.6±2.6	9.7±2.8	9.6±2.7
Polyunsaturated fats (% total kcal)	7.5±1.8	7.8±2.1	7.6±1.9
Fiber (g/day)	17.1±5.2	17.3±5.3	17.2±5.2

Laboratory variables			
Fasting glucose (mg/dL)	94.1±20.2	91.3±17.9	92.7±19.0
Glycated hemoglobin (mmol/mol)	41.4±8.9	40.2±6.8	40.8±7.9
Fasting insulin (μU/mL)	14.0 (6.7)	13.8 (11.4)	14.0 (8.5)
HOMA-IR (mmol/l*μU/mL)	3.1 (2.0)	3.4 (2.8)	3.2 (2.4)
CRP (mg/L)	5.3 (5.4)	5.4 (7.1)	5.3 (6.4)
Total cholesterol (mg/dL)	185.8±41.0	186.4±24.7	186.1±33.7
HDL-cholesterol (mg/dL)	49.8±13.4	47.1±12.2	48.4±12.8
Triglycerides (mg/dL)	105.5 (55.0)	111.5 (56.0)	96.5 (49.0)
Drugs			
Antihypertensive (%)	46.7	43.3	45.0
Hypoglycemic agents (%)	6.7	5.0	5.8
Lipid lowering (%)	13.3	11.7	12.5
Questionnaires			
Satiety score	50 (50)	50 (40)	50 (60)
EuroQoL VAS	61.8±16.3	64.2±17.3	63.0±16.8
EuroQoL health status	0.67±0.21	0.72±0.14	0.70±0.18

Mean ± SD, median (interquartile range)

Table 2. End-of the trial values of variables and comparisons between arms by a linear regression model

	Intervention arm		Control arm				
	End-of the trial value	**Mean delta**	**End-of the trial value**	**Mean delta**	**Adjusted mean difference on delta (β)***	**95%CI**	**P**
Weight (Kg)	102.9±16.3	-6.5	100.8±18.6	-5.6	-0.45	-3.78; 2.88	0.79
BMI (Kg/m^2)	38.7±5.0	-2.4	38.8±5.5	-2.1	-0.24	-1.49; 1.01	0.70
Waist circumference (cm)	115.2±14.7	-6.3	115.8±14.7	-4.9	-1.34	-5.06; 2.37	0.47
Percent body fat	42.5±5.5	-3.1	43.5±6.3	-1.5	-1.38	-2.91; 0.15	0.08
Systolic blood pressure (mmHg)	125.4±15.1	-4.0	129.6±17.5	-2.6	-3.11	-9.28; 3.07	0.32
Diastolic blood pressure (mmHg)	79.9±13.2	-2.3	80.7±8.2	-1.1	-1.03	-5.59; 3.53	0.65
Fasting glucose (mg/dL)	92.0±19.4	-2.3	91.5±18.3	+0.3	-1.17	-8.18; 5.84	0.74

Glycated hemoglobin (mmol/mol)	39.0±6.7	-2.7	38.4±6.7	-1.8	-0.33	-2.3; 1.64	0.74
Fasting insulin (µU/mL)	14.0 (10.2)	-3.7	15.3 (12.8)	-1.5	-1.50	-4.44; 1.43	0.31
HOMA-IR (mmol/l*µU/mL)	3.3 (2.2)	-1.1	3.5 (2.6)	-0.4	-0.44	-1.26; 0.39	0.30
CRP (mg/L)	2.2 (3.0)	-3.5	3.7 (6.0)	-0.7	-2.55	-3.80; -1.31	<0.001
Total cholesterol (mg/dL)	180.9±31.3	-5.3	182.7±33.5	-2.8	-2.07	-14.0; 9.81	0.73
HDL-cholesterol (mg/dL)	53.3±13.3	+4.0	50.9±15.6	+4.9	-0.48	-4.05; 3.09	0.79
Triglycerides (mg/dL)	94.5 (41.5)	-10.0	91.5 (32.0)	-21.6	9.14	-3.61; 21.9	0.16
Satiety score	80 (30)	+19.3	50 (60)	-1.4	19.2	7.71; 30.6	0.001
EuroQoL VAS	73.4±13.7	11.9	66.9±18.2	3.7	6.90	0.63; 13.2	0.03
EuroQoL health status	0.77±0.13	0.11	0.69±0.21	-0.02	0.09	0.02; 0.16	0.01

Mean ± SD, median (interquartile range)
Delta= end-of the trial value – baseline value
*Adjusted for stratification variables (age, gender, BMI) and the baseline value of the variable.

Figure legends

Figure 1

Flow of the study