Long-Term Effects of a Multidisciplinary Treatment of Uncomplicated Obesity on Carotid Intima-Media Thickness

[Q1] **S. Buscemi[1], JA. Batsis[2], S. Verga[1], T. Carciola[1], A. Mattina[1], S. Citarda[1], A. Re[1], M. Arnone[1], L. D'Orio[1], S. Belmonte[1], A. D'Angelo[1] and G. Cerasola[1]**

Obesity is associated with well-known cardiovascular risk factors and a lower life expectancy. This study investigated whether nonoperative nutritional treatment of obesity without comorbidities influenced the carotid intima-media thickness (c-IMT) in the long run. Fifty-four subjects of an original cohort of 251 subjects were re-evaluated 10 years after a medical nutritional treatment (MNT) with cognitive-behavioral approach for uncomplicated obesity. Forty subjects were classified as failure (10-year body weight change >0.5 kg) and 14 (body weight change ≤0.5 kg) as a success of the MNT. Ten years after MNT, c-IMT significantly increased (0.06 ± 0.02 mm; *P* = 0.004) in the failure group and significantly decreased (–0.07 ± 0.03 mm; *P* = 0.027) in the success group. Ten-year change in c-IMT correlated significantly with 10-year change in body weight (*r* = 0.28; *P* = 0.040). Multiple stepwise linear regression analysis demonstrated that age, final BMI, and group (success or failure) influenced independently the 10-year c-IMT. In conclusion, this study is in agreement with the possibility that the successful MNT of obesity may be an effective choice in the long run and seems to indicate that it may be able to reduce the cardiovascular risk as reflected by the change in c-IMT.

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INTRODUCTION

Obesity is associated with increased prevalences of cardiovascular risk factors (1) and a lower life expectancy (2). The increasing prevalence of overweight and obesity are also observed in younger age groups, including adolescents and infants, highlighting the importance of the need to identify management strategies for effective public health interventions. Nonsurgical management of obesity often involves a cognitive-behavioral approach (3,4) aimed at changing unhealthy lifestyles, adopting a healthy dietary model, and increasing regular physical activity. Clinical studies have demonstrated that nonoperative treatments for obesity aimed at maintaining a stable body weight can prevent obesity-related comorbidities (5).

The measurement of carotid intima-media thickness (c-IMT) can add incremental information to risk factor assessment (6). Increased c-IMT is a well-known marker of subclinical atherosclerosis that correlates with cardiovascular risk factors (7), severity of coronary atherosclerosis (8), and has been shown to predict cardiovascular events (9). Despite a need to reduce such obesity-related complications, long-term treatment effects have only been demonstrated for bariatric surgery (10) or for subjects treated medically with impaired glucose tolerance (11). The purpose of this study was to determine whether 1-year medical treatment with cognitive-behavioral approach in obese subjects without comorbidities influences long-term 10-year c-IMT.

METHODS AND PROCEDURES

Patient selection

A total of 251 subjects (age range: 18–65 years; BMI range: 28–40 kg/m^2) were selected among those seen in 1999 at the Obesity and Metabolic Diseases Outpatient Department of the Division of Internal Medicine of the Partinico's Civil Hospital (AUSL 6, Palermo), a community hospital 50 km from Palermo, Italy. We also included a cohort of 90 subjects that answered a public announcement for participating in a previous study (12) designed to estimate the long-term effects of the cognitive-behavioral treatment of obesity. The characteristics of this subgroup are described elsewhere (12). The remaining 161 patients were referred to the hospital spontaneously or by their family doctors.

We excluded subjects at baseline with a diagnosis of diabetes and hypertension, any systemic or end organ disease on the basis of clinical history, use of any pharmacological treatment, physical examination, routine blood tests, and electrocardiogram. Atherosclerotic vascular disease was excluded using echo-doppler examination of the carotid arteries, abdominal aorta, and iliac-femoral-popliteal arteries. Subjects who had

[1]Dipartimento di Medicina Interna, Malattie Cardiovascolari e NefroUrologiche; Facoltà di Medicina, University of Palermo, Palermo, Sicily, Italy; [2]Section of General Internal Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, and Dartmouth College, Hanover, New Hampshire, USA.
Correspondence: Silvio Buscemi (silbus@tin.it)

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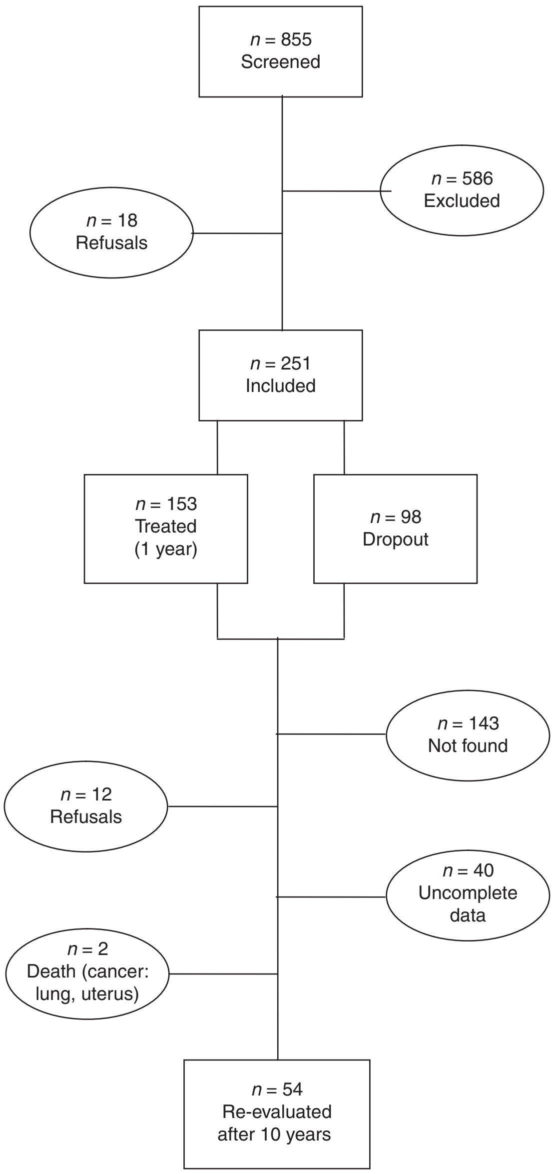
a change of ±2 kg in body weight in the previous 3 months, those who followed a dietary treatment for weight loss during the last year, and pregnant women were excluded. The diagnosis of diabetes was defined according to the American Diabetes Association criteria (13). All subjects underwent a 1-year medical nutritional therapy (MNT) with a cognitive-behavioral approach (14). Subjects were re-evaluated at 10-years between April and June 2009; 54 subjects were interviewed by telephone and subsequently returned to the centre for a clinical examination. The participant flow diagram is presented in **Figure 1**. Informed consent was obtained by all subjects. The study was performed according to the principles of the Helsinki declaration and approved by the Ethics Committee of the University of Palermo and the Committee for the Protection of Human Subjects of Dartmouth College.

Medical nutrition therapy

Participants attended clinical visits weekly for 3 months, then biweekly for the next 3 months and monthly for the subsequent 6 months (20–24 visits in a year). At each visit anthropometric measurements were performed and subjects received nutritional and behavioral counseling. In general, participants regularly met a registered dietitian and psychological support was offered, they could also meet in small groups in the hospital. Furthermore, subjects participated during the first 3 months of treatment to four classroom sessions concerning healthy eating and strategies designed to improve adherence to the nutritional program. Various strategies and problem solving were tailored to each individual at each visit. Suggestions were offered about healthy cooking and preparation of foods according to standardized procedure organized in a booklet program. In general, the diet proposed provided a daily caloric intake of about 20 kcal/kg of actual body weight comprising of ~1,500–2,500 kcal/day with no supplementation (i.e., multivitamin, mineral salts, or antioxidants) was given. Macronutrient distribution provided carbohydrates 55%, lipids 25% (20% saturated, 65% monounsaturated and 15% polyunsaturated), proteins 20% of total calorie intake, a daily intake of about 30 g of fibers and of cholesterol lower than 250 mg. Subjects were counseled to engage in regular physical exercise but no specific activities or interventions were advocated.

Dropout was defined as a patient abandoning treatment during the first 3 months or in subjects whose body weight loss was <5% during this period of time. Success was defined as a weight loss ≥5% (15,16) at 1 year from starting the MNT. Ten years after the MNT, subjects were categorized as "success" if body weight was equal or lower than the baseline value, or as a "failure" if body weight increased ≥0.5 kg. Participants who were initially classified as having dropped-out or those with an unsuccessful initial weight loss attempt were also reconsidered in the analysis at 10 years.



[Q2]

Figure 1 Participants selection flow.

Measurements

Each subject was assessed before beginning the weight loss program. A fasting blood sample was drawn for glucose, cholesterol, high-density lipoprotein cholesterol, triglycerides, uric acid, and other routine biochemical measurements. Height, body weight, systolic and diastolic arterial blood pressure (two measurements obtained at 5 min of interval in seated position) were measured by nurses or dietitians according to standardized procedures. The 54 subjects re-evaluated in 2009 were asked to submit to blood work performed in territorial laboratories during the last 6 months. Fat mass (% body weight) and fat-free mass (kg) were estimated as previously described (17) by means of bioelectrical impedance analysis (BIA-103, RJL, Detroit/Akern, Florence, Italy). Body circumferences were measured at the umbilicus (waist circumference) and at the most prominent buttock level (hip circumference); their ratio (waist-to-hip ratio) was used as an indirect index of body-fat distribution. A 12-lead ECG (Esaote, Genova, Italy) was obtained in all subjects. Images of the right and left extracranial carotid artery walls were obtained in several projections by a high-resolution ultrasonographic 10-MHz linear array probe (Acuson, Malven, PA in 1999; Sonoline G50, Siemens, Germany in 2009); end-diastolic IMT of the far wall of both common carotid arteries was measured 10 mm caudal to the bulb, using two-dimensional longitudinal sections of the vessel and the distance from the first echogenic line to the second echogenic line (three values for each carotid artery using antero-posterior, latero-lateral, and postero-anterior scans); the highest value was considered for calculations (18). A single-blinded experienced physician was responsible for performing the carotid ultrasonographic examinations both in 1999 and in 2009 (S.B.), using a manual method; the between-day intraobserver variability is 4.6% for this operator. The 1999 IMT images were not reread in 2009 since the registrations (VHS) were not [Q3] available.

Statistical analysis

All data are expressed as mean ± s.e.m. The variables considered in the study were normally distributed on the basis of the Shapiro–Wilk test; specifically, for 10-year c-IMT the coefficient of 0.966 with a P = [Q4] 0.102 was obtained. The Student's *t*-test for unpaired data was used to compare the means of two groups. The χ^2 test was applied to compare frequencies between groups. The Student's *t*-test for paired data was used to compare changes with time of measures in the same group. The relationships between variables were tested by the Pearson's

Table 1 Physical and clinical characteristics of obese subjects who underwent medical nutritional treatment and divided in two groups on the basis of successful weight loss at 10 years

	10-year weight reduction						
	Success group			Failure group			
	Initial	Final	P^a	Initial	Final	P^a	$P^{a,b}$
M/F	2/12			8/32			
Age (years)	41.2 ± 3.7			40.5 ± 1.6[c]			
Smokers, *n* (%)	3 (21.4)	3 (21.4)	0.645	12 (30.0)[c]	9 (22.5)[d]	0.611	
Hypertension, *n* (%)	3 (21.4)	7 (50.0)	0.237	3 (7.5)[c]	18 (45.0)[d]	<0.001	
Diabetes, *n* (%)	0	1 (7.1)	1.000	0[c]	6 (15.0)[d]	0.034	
Subjects on anti-hypertensives, *n* (%)	0	7 (50.0)	0.009	0[c]	18 (45.0)[d]	<0.001	
Subjects on antidiabetics, *n* (%)	0	1 (7.1)	1.000	0[c]	5 (12.5)[d]	0.065	
Body weight (kg)	90.1 ± 6.0	84.2 ± 5.3	0.012	85.2 ± 2.5[c]	94.9 ± 3.1[d]	<0.001	<0.001
BMI (kg/m^2)	35.9 ± 2.6	33.6 ± 2.4	0.010	33.2 ± 0.8[c]	37.0 ± 1.1[d]	<0.001	<0.001
FM %	36.1 ± 1.9	35.2 ± 2.3	0.343	33.9 ± 1.0[c]	39.6 ± 1.3[d]	<0.001	0.001
Waist circumference (cm)	111 ± 6	106 ± 5	0.021	106 ± 2[c]	113 ± 3[d]	<0.001	<0.001
Blood concentration of							
glucose (mg/dl)	94 ± 4	104 ± 16	0.498	91 ± 2[c]	92 ± 2[d]	0.397	0.913
Total cholesterol (mg/dl)	199 ± 12	191 ± 11	0.324	217 ± 6[c]	212 ± 6[d]	0.286	0.814
HDL-cholesterol (mg/dl)	41.7 ± 2.6	45.5 ± 2.6	<0.047	45.8 ± 1.5[c]	46.9 ± 1.8[d]	0.501	0.273
Triglycerides (mg/dl)	156 ± 35	140 ± 29	0.208	115 ± 10[c]	127 ± 8[d]	0.080	0.053
LDL-cholesterol (mg/dl)	126 ± 11	118 ± 11	0.278	148 ± 6[c]	139 ± 5[d]	0.119	0.899
Uric acid (mg/dl)	5.3 ± 0.3	5.1 ± 0.3	0.413	4.7 ± 0.2[c]	5.1 ± 0.2[d]	0.033	0.048
Blood pressure							
Systolic (mm Hg)	133 ± 7	133 ± 6	0.957	131 ± 3[c]	138 ± 3[d]	0.004	0.257
Diastolic (mm Hg)	84 ± 3	78 ± 3	0.108	81 ± 2[c]	82 ± 2[d]	0.322	0.060
Carotid-IMT max (mm)	0.71 ± 0.04	0.64 ± 0.03	<0.027	0.66 ± 0.02[c]	0.72 ± 0.03[d]	0.004	0.001

All values expressed as mean ± s.e.m., or count (%).
FM, fat mass; HDL, high-density lipoproteins; IMT, intima-media thickness; LDL, low density lipoproteins.
[a]Student's paired *t*-test or Pearson's χ^2 test, as appropriate. [b]Inter-group (success vs. failure) differences of the changes (final minus initial) of continuous variable values.
[c]*P* = NS vs. correspondent initial value in the success group. [d]*P* = NS vs. correspondent final value in the success group.

coefficients of correlation. Exploratory analyses were performed to assess the predictors of 10-year c-IMT but also to assess the strength and independency of associations between variables using multiple regression analysis (stepwise backward selection). A *P* value of <0.05 was considered as statistically significant. We utilized SYSTAT statistical software (Windows version, release 12.0; Systat Software, San Jose, CA) for all analyses.

RESULTS

A total of 251 subjects underwent MNT for obesity at baseline and 98 (39%) dropped-out (**Figure 1**); the remaining 153 (61%) subjects completed the treatment. Among completers, in 112 subjects (73.2%) a successful weight loss was observed at 6 months. Twelve months after starting the MNT, successful weight loss was observed in 109 (71.2%) subjects; in this group, the average weight reduction was 9.8% (−9 ± 0.4 kg) as compared to the 3.1% (−2.7 ± 0.2 kg) in the group where the MNT was considered a failure (*P* < 0.001). Ten years after the MNT, 40 subjects were classified as failure and 14 as a success. Five subjects who were initially classified as dropout were included in the success group 10 years later, 18 dropout subjects were included in the failure group. The number of treatments of hypocaloric diets (either prescribed or self-prescribed) between the two observation periods (1999–2009), did not differ between the two groups (failure group: 1.7 ± 0.2 vs. success group: 1.7 ± 1.3; *P* = 0.933). The demographic and clinical characteristics of the two subgroups (success and failure groups) at baseline and at 10 years are reported in **Table 1**. No clinical cardiovascular disease manifestations were reported in either group during follow-up, no new carotid plaques were observed at 10-year echographic evaluation. Ten years after MNT, c-IMT significantly increased (0.06 ± 0.02 mm; *P* = 0.004) in the failure group and significantly decreased (−0.07 ± 0.03 mm; *P* = 0.027) in the success group. Ten-year change in c-IMT correlated significantly with 10-year change in body weight (**Figure 2**). The 10-year c-IMT was significantly correlated with the 10-year BMI (*r* = 0.32; *P* = 0.017) but not with the 10-year body weight (*r* = 0.26; *P* = 0.057). **Table 2** reports the independent predictors of the 10-year c-IMT. The 1-year success of medical nutrition therapy did not predict the 10-year c-IMT (*P* = 0.374) when it was entered in the multiple regression analysis instead of the 10-year success.

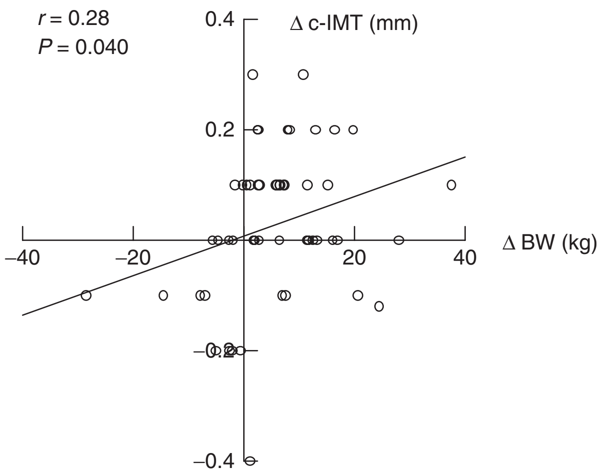


Figure 2 Correlation between the 10-years change of body weight (Δ BW) and the 10-years change of carotid intima-media thickness (Δ c-IMT).

Table 2 Multiple stepwise linear regression analysis (backward selection).

Variable	β-Coefficient	*P*
10-year carotid-IMT		
Age	0.007	<0.001
10-year BMI	0.007	<0.01
Group (1 = success, 2 = failure)	0.082	<0.05
Sex (1 = male, 2 = female)	—	0.939

IMT, intima-media thickness.

DISCUSSION

Strategies aimed at reducing body weight generally produce favorable short-term results but maintaining such weight loss often proves difficult to sustain in the long term (19–21). Furthermore, it is unknown if long-term effects of MNT effectively reduces both metabolic and cardiovascular morbidity or mortality. Our study demonstrates that the c-IMT is lower in subjects who maintained or lost weight at 10 years after a MNT, compared to an increase in c-IMT in those who increased their body weight. If c-IMT is an accepted measure of subclinical atherosclerosis that correlates with cardiovascular events (9,22,23), then the study results are in agreement with the hypothesis that long-term weight loss may be associated with a reduction of cardiovascular risk especially in those subjects whose c-IMT remained under the value of 0.9 mm that is actually considered the cutoff of normality for c-IMT (24).

The results concerning the 10-year c-IMT variation may in part be explained by the observation that in the failure group, the incidence of diabetes was double than that observed in the success subgroup, and that systolic blood pressure and uric acid levels increased significantly. On the contrary, the high-density lipoprotein cholesterol blood levels increased significantly in the success subgroup. Despite the 10-year incidence of both hypertension and diabetes was significantly lower (**Table 1**) in the success group, the cohort size is numerically too small to consider this result. However, it seems plausible to hypothesize that MNT of obesity is able to prevent diabetes and hypertension in this at-risk cohort and consequently influence favourably the c-IMT. We cannot discriminate on the basis of our results if the favorable changes of c-IMT in the success group with respect to the failure group are due to the changes in body weight or, rather, if they are in consequence of a more healthy habitual nutrition. The correlation between 10-year weight change with c-IMT change does not resolve this problem because body weight change may reflect nutritional changes. However, the multivariate analysis demonstrates that the group (failure vs. success) has an influence on the 10-year c-IMT which is independent from age and BMI suggesting that improving lifestyle measures *per se* may have a favorable impact on the c-IMT. In addition, we did not observe any collinearity among these confounders as well.

It was recently shown that intensifying behavioral treatments have effects on weight loss in the middle term comparable to those obtained by means of the surgical treatment of obesity (25). Our study demonstrates in a small patient cohort, that MNT of obesity using a cognitive-behavioral approach is successful (about 26% of treated subjects) even in the long-term (10 years) in obese nondiabetic subjects as demonstrated in other studies (26,27). These results highlight the limited efficacy of lifestyle modifications on rates of weight loss and certainly much improvement would be needed from a population-health management standpoint to further reduce these persistently high rates, however even small changes may impact c-IMT. Successful MNT of obesity can be defined by improvements in metabolic and cardiovascular risk factors, and quality of life. These objectives can be obtained even through modest amounts of weight loss (5–10% loss of initial body weight) (15,16,28), and further research should support identifying successful predictors of weight loss. In addition, over a 10-year period, although goals are for weight loss, one can consider maintenance of weight to be a success in of itself (29,30), as data have demonstrated that weight does increase for every decade of life (31).

A surprising result of this study is that the initial dropout did not influence the final success 10 years after the MNT. It is well described (32–34) that a short lasting nutritional treatment may give effects measured in the long run, this phenomenon has been indicated as vaccination effect of the initial treatment (35). The two subgroups at 10 years (failure and success) did not differ for the number of dietary treatments after the MNT of 1999, therefore we are induced to conclude that the vaccination effect is possible even in the case of initial dropout.

This study has inherent limitations. Only a limited part of the initial cohort was re-evaluated at 10 years which reduces study power leading to wide variations in prevalences and means between groups, including gender associations with c-IMT. However, it should be considered that larger cohorts are difficult to be obtained when considering the MNT of uncomplicated obesity in the long-term. In fact, the number of subjects considered in our study is similar to that reported by other studies that investigated the maintenance of weight loss following dietary treatment of uncomplicated obesity even with a shorter follow-up than in our study (36–39). Another major limitation is that >50% of subjects were lost to follow-up. This is somewhat unusual and high for a prospective study; however, we encountered problems in identifying patients' home phone numbers and home addresses due largely to an increased usage of mobile telephones, and 30% reduction in landlines, leading to the tracking of such patients difficult (40,41). In addition, there was a tendency of high emigration (regional or national) in the study area (Partinico) (42). We acknowledge such numbers are difficult to identify and account for.

The baseline cohort was not homogeneously enrolled since subjects might be referred by their family doctors or voluntarily answered to our announcement introducing additional bias. However, we feel that this latter limitation did not influence the 10-year results concerning c-IMT changes and the success of MNT given the fact that the percentages of the two different recruited subjects were similar between failure and success group (data not shown). Although we encouraged physical activity as it impacts our primary outcomes, it was not systematically measured which may impact our results.

Other possible limitations may have affected this study. Although automated methods are available currently to ascertain c-IMT values and reduce measurement drift (43,44), the original images were not originally stored for retrospective review nor were they available or validated in 1999, and hence manual methods were used for measurement at both [Q5] time points. However, by using manual methods by the same observer, we likely mitigated observer and measurement bias, which would otherwise be incorporated if different methods have been used. Furthermore, the probability of errors are likely equally distributed between all participants. Other studies have reported reading variability with manual analyzing system and with different operators that is around 4%, a value that induces to consider as valid the 10-year c-IMT differences that we found to be higher than ±9% (–9.6% in the success vs. 9.1% in the failure group) in our groups. In addition, there is some evidence that validates that well-standardized measurements by trained technicians are probably as good as automated methods (45). We encountered issues pertaining to outdating of the device as well, making it challenging to retrospectively analyze the data or test reproducibility. We note that there are studies that have demonstrated <3% disagreement between such methods (46). Interlaboratory variability may indeed lead to inherent measurement bias thus limiting considerably the possibility of comparing the change of these variables with time. Finally, as the group of patients were young at baseline, it is not unexpected that there were few cardiovascular disease manifestations or deaths noted.

In conclusion, these results highlight the limited efficacy of lifestyle modifications on rates of weight loss and certainly much improvement would be needed from a population-health management standpoint to further reduce these persistently high rates. However even small changes appear to impact c-IMT. Further long-term studies including larger cohorts and clinical outcomes are necessary to obtain definitive answers.

DISCLOSURE

The authors declared no conflict of interest.

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