

# Effect of Lifestyle Changes on Erectile Dysfunction in Obese Men

## A Randomized Controlled Trial

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**E**RECTILE DYSFUNCTION IS AN important cause of decreased quality of life in men,<sup>1-3</sup> and may affect an estimated 30 million men in the United States.<sup>3</sup> In the Health Professionals Follow-up Study, moderate to severe erectile dysfunction was reported by 12% of men younger than 59 years; 22% of men aged 60 to 69 years; and 30% of men older than 69 years.<sup>4</sup>

Moreover, several modifiable lifestyle factors, including physical activity and leanness, were associated with maintenance of erectile function. For instance, men with a body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) higher than 28.7 have a 30% higher risk for erectile dysfunction than those with a normal BMI ( $\leq 25$ ).<sup>4</sup> The prevalence of overweight or obesity in men reporting symptoms of erectile dysfunction may be as high as 79%,<sup>5</sup> although vascular risk factors commonly associated with obesity also may play an important role.<sup>6</sup>

**See also p 3011 and Patient Page.**

**Context** Healthy lifestyle factors are associated with maintenance of erectile function in men.

**Objective** To determine the effect of weight loss and increased physical activity on erectile and endothelial functions in obese men.

**Design, Setting, and Patients** Randomized, single-blind trial of 110 obese men (body mass index  $\geq 30$ ) aged 35 to 55 years, without diabetes, hypertension, or hyperlipidemia, who had erectile dysfunction that was determined by having a score of 21 or less on the International Index of Erectile Function (IIEF). The study was conducted from October 2000 to October 2003 at a university hospital in Italy.

**Interventions** The 55 men randomly assigned to the intervention group received detailed advice about how to achieve a loss of 10% or more in their total body weight by reducing caloric intake and increasing their level of physical activity. Men in the control group (n=55) were given general information about healthy food choices and exercise.

**Main Outcomes Measures** Erectile function score, levels of cholesterol and triglycerides, circulating levels of interleukin 6, interleukin 8, and C-reactive protein, and endothelial function as assessed by vascular responses to L-arginine.

**Results** After 2 years, body mass index decreased more in the intervention group (from a mean [SD] of 36.9 [2.5] to 31.2 [2.1]) than in the control group (from 36.4 [2.3] to 35.7 [2.5]) ( $P < .001$ ), as did serum concentrations of interleukin 6 ( $P = .03$ ), and C-reactive protein ( $P = .02$ ). The mean (SD) level of physical activity increased more in the intervention group (from 48 [10] to 195 [36] min/wk;  $P < .001$ ) than in the control group (from 51 [9] to 84 [28] min/wk;  $P < .001$ ). The mean (SD) IIEF score improved in the intervention group (from 13.9 [4.0] to 17 [5];  $P < .001$ ), but remained stable in the control group (from 13.5 [4.0] to 13.6 [4.1];  $P = .89$ ). Seventeen men in the intervention group and 3 in the control group ( $P = .001$ ) reported an IIEF score of 22 or higher. In multivariate analyses, changes in body mass index ( $P = .02$ ), physical activity ( $P = .02$ ), and C-reactive protein ( $P = .03$ ) were independently associated with changes in IIEF score.

**Conclusion** Lifestyle changes are associated with improvement in sexual function in about one third of obese men with erectile dysfunction at baseline.

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Obesity is an independent risk factor for cardiovascular disease,<sup>7</sup> and is associated with elevated levels of sev-

eral proinflammatory cytokines, such as interleukin 6 (IL-6), interleukin 8 (IL-8), and C-reactive protein (CRP),

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a marker of inflammation.<sup>8-11</sup> Markers of low-grade inflammation are positively associated with endothelial dysfunction in human obesity.<sup>8,10</sup> Erectile and endothelial dysfunctions may have some shared pathways<sup>12</sup> through a defect in nitric oxide activity, which may be inhibited through age-, disease-, and behavioral-related pathways. In theory, intervention in modifiable health behaviors, especially reducing body weight and increasing physical activity, may reduce the risk of both erectile dysfunction and endothelial dysfunction in obese men, but this hypothesis has not been tested.

The aim of this randomized controlled trial of obese men with erectile dysfunction was to determine if lifestyle changes designed to obtain a sustained and long-term reduction in body weight ( $\leq 10\%$  of initial weight maintained for 2 years) and an increase in physical activity positively affect erectile and endothelial functions.

## METHODS

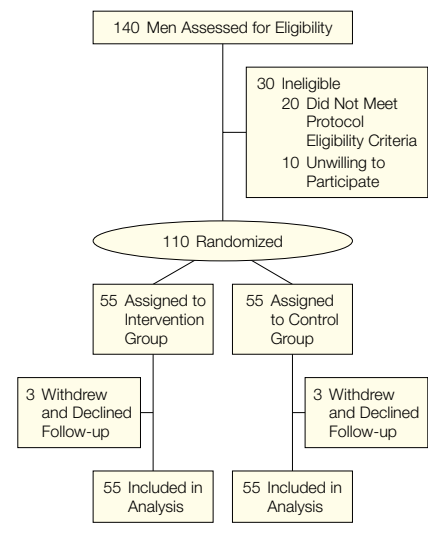
Obese men with erectile dysfunction, aged 35 to 55 years, were recruited from the outpatient department for weight loss at the Second University of Naples, Naples, Italy, in October 2000. The trial ended in October 2003. Erectile function was assessed by completing questions 1 to 5 on the International Index of Erectile Function (IIEF), which is a multidimensional questionnaire.<sup>13</sup> The 5 questions asked were (1) How often were you able to get an erection during sexual activity?; (2) When you had erections with sexual stimulation, how often were your erections hard enough for penetration?; (3) When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?; (4) During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?; and (5) During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse? The IIEF score represents the sum of questions 1 to 5, with a maximum score of 25; a score of 21 or less indicates erectile dysfunction.

We assessed 140 men with IIEF scores lower than 22 to determine eligibility. These men had no evidence of participation in diet reduction programs within the last 6 months and had completed a health and medical history questionnaire, which served as a screening tool. Exclusion criteria were diabetes mellitus or impaired glucose tolerance (plasma glucose levels of 140-200 mg/dL [7.8-11.1 mmol/L] 2 hours after a 75-g oral glucose load), impaired renal function, including macroalbuminuria, pelvic trauma, prostatic disease, peripheral or autonomic neuropathy, hypertension (blood pressure  $> 140/90$  mm Hg), cardiovascular disease, psychiatric problems, use of drugs or alcohol abuse ( $\geq 500$  g of alcohol per week in the last year). After the exclusion of 30 ineligible men, 110 obese, sedentary ( $< 1$  hour per week of physical activity) men were enrolled in the trial. The study was approved by the institutional committee of ethical practice at the Second University of Naples. Participants provided informed written consent for voluntary, unpaid participation.

Men were randomly assigned to either the intervention or control group using a computer-generated random number sequence (FIGURE 1). Allocation was concealed in sealed study folders that were maintained at a central, secure location until after informed consent was obtained. The nurses who scheduled the study visits did not have access to the randomization list. However, the staff members involved in the intervention had to be aware of the group assignment; thus, the study was only partially blinded. Laboratory staff did not know the participants' group assignments.

Men in the intervention group were given detailed advice about how to achieve a reduction in total body weight of 10% or more. The program consisted of instruction regarding reducing caloric intake, setting goals, and self-monitoring (food diaries) through a series of monthly small group sessions. Behavioral and psychological counseling was also offered. The mean daily caloric intake was 1700 kcal for

**Figure 1.** Flow of Patients Through the Trial



the first year and 1900 kcal for the second year. The recommended composition of the dietary regimen per 1000 kcal was carbohydrates, 50% to 60%; proteins, 15% to 20%; total fat, less than 30%; saturated fat, less than 10%; mono-unsaturated fat, 10% to 15%; polyunsaturated fat, 5% to 8%; and fiber, 18 g. Dietary advice was tailored to each man on the basis of food records collected on 3 nonconsecutive days and completed the week before the meeting with the nutritionist. These men also received individual guidance on increasing their level of physical activity, mainly walking, but also swimming or aerobic games (ie, football, baseball, soccer). Men were in the program for 2 years. They had monthly sessions with the nutritionist and exercise trainer during the first year and bimonthly sessions during the second year. Compliance with the program was assessed by attendance at the meetings and completion of the food diaries.

Men in the control group were given general oral and written information about healthy food choices and exercise at baseline and at subsequent bimonthly visits, but no specific individualized program was provided.

Height and weight were recorded with participants wearing lightweight clothing and no shoes using a Seca 200

scale (Seca, Hamburg, Germany) with attached stadiometer. Waist-to-hip ratio (WHR) was calculated as waist circumference in centimeters divided by hip circumference in centimeters. Twenty-four hour nutrient intakes were calculated with food-composition tables and patients' weekly food diaries. All men were asked to complete a record of food intake for 3 days to assess dietary adherence and to record occupational, household, and leisure-time physical activity to assess exercise activity. Foods were measured using standard measuring cups and spoons and weight-approximation diagrams. No participants in either group took any drug specific for erectile dysfunction at baseline (exclusion criterion); however, if during the course of the study there was a need for such use, this was discussed and recorded.

Endothelial function was assessed with the L-arginine test, as previously described.<sup>14</sup> Briefly, an intravenous bolus of 3 g of L-arginine (10 mL of a 30%

solution of L-arginine monochloride), the natural precursor of nitric oxide, was injected intravenously within 60 seconds. Blood pressure and platelet aggregation response to 1.25  $\mu$ mol of adenosine diphosphate were measured before L-arginine injection and after 10 minutes. L-arginine mimics some of the effects of nitric oxide, including vasodilatation and antiplatelet activity; because the vascular effects of L-arginine are thought to derive from metabolic conversion to nitric oxide, the L-arginine test has been used for evaluating endothelial function.<sup>15</sup> In our laboratory, following the L-arginine bolus (difference between basal and 10-minute values) in a matched control group of nonobese men ( $n=50$ ), there was a decrease in platelet aggregation by 13% and a mean (SD) decrease in blood pressure by 6.5 (1.5) mm Hg.<sup>4</sup>

Assays for serum levels of total and high-density lipoprotein cholesterol, triglycerides, and glucose were performed in the hospital's chemistry labo-

ratory. Plasma insulin levels were assayed by radioimmunoassay (Ares, Serono, Italy). Serum samples for cytokine and CRP levels were stored at  $-80^{\circ}\text{C}$  prior to being assayed. Serum concentrations of IL-6 and IL-8 were determined in duplicate using a highly sensitive, quantitative sandwich enzyme assay (Quantikine HS, R&D Systems, Minneapolis, Minn). High-sensitivity CRP was assayed by immunonephelometry on Behring Nephelometer 2 (Dade Behring, Deerfield, Ill). In our laboratory, the medians (interquartile ranges) for these values were 2.1 pg/mL (0.3-5.2 pg/mL) for IL-6; IL-8, 3.1 pg/mL (0.8-6.2 pg/mL); and CRP, 0.7 mg/L (0.2-3.2 mg/L). These values are based on 50 healthy, nonobese men who were matched to obese men for age and metabolic characteristics.

Data are presented as mean (SD) unless otherwise indicated and were analyzed using the intention-to-treat principle. We compared baseline data using a *t* test for continuous variables and the Wilcoxon test for IL-6, IL-8, and CRP. We compared risk factors and nutrient intake after 2 years using a *t* test based on the values at the end of follow-up and a *t* test based on differences from baseline. Results of the analysis omitting patients lost during follow-up did not differ from that including the last available records; data are therefore shown for the analysis that includes all men as randomized. Spearman rank correlation coefficients were used to quantify the relationships between metabolic variables and cytokine levels. The effects of intervention on IIEF score, indices of endothelial function, and cytokine levels were tested by means of paired *t* tests and a Wilcoxon matched test. The  $\chi^2$  test was used for comparing proportions of men in the 2 groups that obtained erectile function after treatment. Multivariate regression analysis tested the independent association and contribution of changes in BMI, WHR, physical activity, indices of endothelial function, and plasma cytokine concentrations with the dependent variable (changes in IIEF score), and also included baseline IIEF score as a covariate.  $P<.05$  was consid-

**Table 1.** Characteristics of the Study Participants\*

Characteristic	Intervention Group (n = 55)	Control Group (n = 55)	P Value
Age, y	43.5 (4.8)	43 (5.1)	.62
Weight, kg	103 (9.4)	101 (9.7)	.55
Body mass index†	36.9 (2.5)	36.4 (2.3)	.65
Waist-to-hip ratio	1.02 (0.09)	1.01 (0.09)	.75
Erectile dysfunction score‡	13.9 (4)	13.5 (4)	.55
Blood pressure, mm Hg			
Systolic	127 (7.5)	128 (7.7)	.49
Diastolic	86 (3.7)	85 (4.1)	.48
Cholesterol level, mg/dL			
Total	213 (32)	210 (29)	.45
High-density lipoprotein	39 (10)	40 (9)	.76
Triglycerides, mg/dL	169 (56)	174 (51)	.23
Glucose, mg/dL	103 (10)	104 (11)	.77
Insulin, $\mu\text{U}/\text{mL}$	21 (8)	19 (7)	.35
Interleukin, pg/mL§			
6	4.5 (1.9-9)	4.4 (2-8.6)	.39
8	5.3 (2.3-10)	5.0 (2.2-9.7)	.45
C-reactive protein, mg/L§	3.3 (1.2-8.1)	3.4 (1.2-8.3)	.37
Response to L-arginine			
Platelet aggregation, %	-4 (2.2)	-3.6 (2.1)	.19
Mean blood pressure, mm Hg	-2.5 (1.3)	-2.4 (1.4)	.27

SI conversion factors: To convert total cholesterol and high-density lipoprotein cholesterol from mg/dL to mmol/L, multiply by 0.0259; glucose from mg/dL to mmol/L, multiply by 0.0555; insulin from  $\mu\text{U}/\text{mL}$  to pmol/L, multiply by 7.175; and triglycerides from mg/dL to mmol/L, multiply by 0.0113.

\*Data are presented as mean (SD) unless otherwise indicated.

†Calculated as weight in kilograms divided by the square of height in meters.

‡Based on the International Index of Erectile Function (range, 1-25).

§Data are presented as median (interquartile range).

ered statistically significant. All analysis were conducted using SPSS statistical software (version 9.0, SPSS Inc, Chicago, Ill).

**RESULTS**

One hundred ten men were randomly assigned to the intervention (n=55) or control group (n=55) (Figure 1). Both groups were comparable and relatively healthy (TABLE 1). The prevalence of smokers was similar in the 2 groups: 27% in the intervention group and 31% in the control group (P=.34). All men were obese, with BMI values ranging from 30 to 49. The mean erectile function score was also comparable between groups with values ranging from 7 to 19 in the intervention group and from 7 to 20 in the control group. As expected for an obese male population, serum IL-6, IL-8, and CRP levels were higher than previously reported in nonobese men.<sup>8,11</sup> Spearman rank correlation coefficients between IIEF score and metabolic variables are shown in TABLE 2. Univariate correlations are provided, but they were scarcely affected by adjustment for age. Erectile function score was positively associated with mean blood pressure responses to L-arginine and negatively associated with BMI, WHR, and CRP.

After 2 years of follow-up, there were 3 dropouts in the intervention group and 3 in the control group, all of which occurred after 24 weeks of follow-up. Dropouts from the intervention group

showed a decrease in body weight after 24 weeks of follow-up, suggesting that they were adhering to the lifestyle changes. Five men in the control group and 4 in the intervention group used pharmacological therapy for erectile dysfunction (phosphodiesterase type 5 inhibitors) during the course of the study; however, excluding these men in the analysis did not affect the results, and therefore data are pooled for all participants.

Baseline data showed no important difference in nutrient intake between the 2 groups (TABLE 3). After 2 years, patients in the intervention group consumed a greater percentage of calories from complex carbohydrates, protein, and monounsaturated fat; had a greater intake of fiber; had a lower ratio of omega-6 to omega-3 fatty acids; and had lower intakes of total calories, saturated fat, and cholesterol (Table 3). The level of physical activity increased more in the intervention group (from 48 [10] to 195 [36] min/wk) than in the control group (from 51 [9] to 84 [28] min/wk; P<.001).

After 2 years, men in the intervention group had significant decreases in body weight, BMI, WHR, blood pressure, levels of glucose, insulin, total cholesterol and triglycerides, but a significant increase in high-density lipoprotein cholesterol (TABLE 4). There was no significant change in these pa-

rameters among men in the control group (Table 4). Serum concentrations of IL-6 and CRP were significantly reduced in the intervention group compared with the control group. Erectile function score improved in the intervention group, but remained stable in the control group (FIGURE 2). Seventeen men in the intervention group and 3 in the control group (P=.001) reported an IIEF score of 22 or higher. Thus, 31% of men in the intervention group regained sexual function.

In the intervention group, changes in IIEF score were related to the reduc-

**Table 2.** Correlations With Erectile Dysfunction Score in Obese Men (N = 110)

Characteristic	Correlation Coefficient	P Value
Weight	-0.45	.01
Body mass index	-0.37	.02
Waist-to-hip ratio	-0.49	.007
Cholesterol level Total	-0.15	.06
High-density lipoprotein	0.08	.09
Triglycerides	-0.09	.12
Glucose	-0.08	.15
Insulin	-0.04	.24
Interleukin* 6	-0.10	.06
8	-0.17	.05
C-reactive protein*	-0.25	.03
Response to L-arginine Platelet aggregation	0.14	.06
Mean blood pressure	0.28	.03

\*Log-transformed data.

**Table 3.** Nutrient Indices at Entry to Study and After 2 Years

Nutrient	Intervention Group (n = 55)			Control Group (n = 55)			Corrected Difference in Mean Change at 2 Years (95% CI)	P Value at 2 Years
	Mean (SD)		P Value	Mean (SD)		P Value		
	Baseline	2 Years		Baseline	2 Years			
Total energy, kcal/d	2340 (205)	1950 (168)	.01	2390 (215)	2340 (174)	.07	-340 (-520 to -160)	.01
Carbohydrates, %								
Regular	57 (2.5)	55 (2.9)	.01	57 (2.1)	57 (2.9)	.56	-2 (-3.4 to -0.6)	.02
Complex	43 (3.7)	50 (2.5)	.001	39 (2.4)	40 (2.2)	.15	6 (2 to 4)	.001
Fiber, g/d	15 (1.5)	25 (1.7)	.01	15 (1.6)	16 (1.8)	.10	9 (5 to 13)	.009
Protein, %	13 (1.9)	16 (1.7)	.02	13 (1.8)	14 (1.7)	.08	2.0 (0.5 to 3.5)	.04
Fat, %	30 (2.6)	29 (2.7)	.06	30 (3.3)	29 (2.9)	.59	0 (-1 to 1)	.90
Saturated	14 (2.5)	9 (1.3)	.01	14 (2.4)	14 (2.5)	.90	-5 (-9 to -1)	.001
Monounsaturated	9 (1.4)	14 (1.7)	.01	10 (1.6)	10 (1.4)	.95	5 (1.5 to 8.5)	.01
Polyunsaturated	7 (1.2)	6 (0.9)	.07	6 (1.1)	5 (0.8)	.09	0 (-1.5 to 1.5)	.88
Ratio of omega-6 to omega-3 fatty acid	12 (2.4)	6 (0.9)	.001	13 (2.1)	12 (1.9)	.08	-5 (-9 to -1)	.001
Cholesterol, mg/d	360 (39)	276 (26)	.01	356 (40)	327 (31)	.05	-53 (-95 to -11)	.02

**Table 4.** Clinical and Metabolic Characteristics of the Study Participants after 2 Years\*

Characteristic	Intervention Group (n = 55)			Control Group (n = 55)			Corrected Difference in Mean Change at 2 Years (95% CI)	P Value at 2 Years
	2 Years	Mean Change	P Value	2 Years	Mean Change	P Value		
Weight, kg	88 (8.5)	-15	<.001	99 (9.2)	-2	.27	-13 (-18 to -11)	.007
Body mass index†	31.2 (2.1)	-5.7	<.001	35.7 (2.5)	-0.7	.19	-5 (-7.5 to -2.5)	<.001
Waist-to-hip ratio	0.93 (0.08)	-0.09	<.001	1.00 (0.09)	-0.01	.56	-0.08 (-0.12 to -0.06)	.01
Erectile dysfunction score‡	17 (5)	3.01	<.001	13.6 (4.1)	0.1	.89	3 (1.2 to 4.8)	.008
Blood pressure, mm Hg								
Systolic	124 (7.4)	-3	.04	127 (7.8)	-1	.50	-2 (-3 to -1)	.01
Diastolic	82 (3.6)	-4	.02	85 (4.5)	0	.98	-4 (-6.5 to -1.5)	.009
Cholesterol level, mg/dL								
Total	202 (24)	-11	.04	212 (31)	2	.72	-13 (-23 to -3)	.02
High-density lipoprotein	48 (9)	9	.001	40 (9)	0	.99	9 (5 to 13)	.01
Triglycerides, mg/dL	150 (45)	-19	.04	170 (47)	-4	.67	-15 (-29 to -1)	.05
Glucose, mg/dL	95 (8)	-8	.02	103 (11)	-1	.34	-7 (-12 to -2)	.02
Insulin, µU/mL	14 (5)	-7	.04	17 (7)	-2	.09	-5 (-9 to -1)	.04
Interleukin, pg/mL§								
6	3.1 (0.9-7)	-1.4	.04	4.5 (2.1-8.8)	0.1	.67	-1.5 (-2.9 to 0.3)	.03
8	4.1 (1.3-8.9)	-1.2	.05	4.7 (1.4-8.4)	-0.3	.23	-0.9 (-2.0 to 0.3)	.07
C-reactive protein, mg/L§	1.9 (0.9-7.1)	-1.4	.01	3.4 (1.3-8.2)	0	.67	-1.4 (-2.5 to -0.3)	.02
Response to L-arginine								
Platelet aggregation, %	-11 (4.8)	-7	.01	-4.3 (3.2)	-0.7	.17	-6.3 (-9.3 to -3.3)	.02
Mean blood pressure, mm Hg	-5.1 (1.9)	-2.6	.001	-2.6 (1.5)	-0.2	.47	-2.4 (-3.2 to -1.6)	.02

SI conversion factors: To convert total cholesterol and high-density lipoprotein cholesterol from mg/dL to mmol/L, multiply by 0.0259; triglycerides from mg/dL to mmol/L, multiply by 0.0113; glucose from mg/dL to mmol/L, multiply by 0.0555; and insulin from µU/mL to pmol/L, multiply by 7.175.

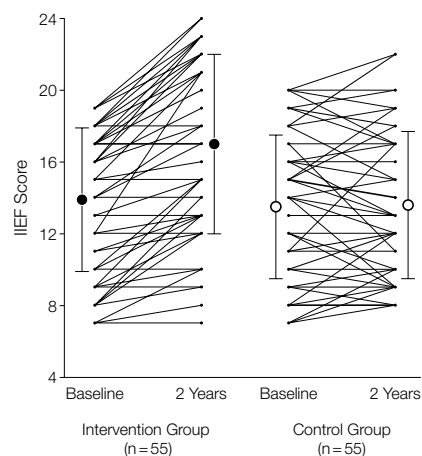
\*Data are presented as mean (SD) unless otherwise indicated.

†Calculated as weight in kilograms divided by the square of height in meters.

‡Based on the International Index of Erectile Function scale.

§Data are presented as median (interquartile range).

**Figure 2.** Individual Changes in Erectile Function Score of Obese Men



IIEF indicates International Index of Erectile Function. Data markers with error bars indicate mean (SD).

tions in BMI ( $r = -0.35$ ;  $P = .02$ ) and increases in the level of physical activity ( $r = 0.40$ ,  $P = .02$ ). The relationship between BMI and IIEF score was continuous in this population, with no evidence of a threshold effect. These

associations remained statistically significant after performing a multivariate analysis in which IIEF score was the dependent variable and BMI, WHR, level of physical activity, indices of endothelial function, baseline IIEF score, and serum CRP concentrations were the independent variables. Body mass index (25% of the variance;  $P = .02$ ), physical activity (26% of the variance;  $P = .02$ ), and CRP (18% of the variance;  $P = .03$ ) were independent predictors of IIEF score and explained almost 68% of the variability in score changes.

**COMMENT**

In this study, we tested the hypothesis that lifestyle changes aimed at reducing body weight and increasing physical activity would induce amelioration of erectile and endothelial functions in obese men. The physiological rationales underlying this hypothesis are that healthy lifestyle factors are associated with maintenance of good erectile function in men<sup>4</sup>; obe-

sity has been positively associated with endothelial dysfunction and increased serum concentrations of vascular inflammatory markers<sup>9,10</sup>; and both endothelial and erectile dysfunction may share some common metabolic and vascular pathways that may be influenced by behavioral-related pathways.<sup>16,17</sup>

Obese men with erectile dysfunction had evidence of abnormal endothelial function, which was indicated by reduced blood pressure and platelet aggregation responses to L-arginine and elevated serum concentrations of markers of low-grade inflammation, such as IL-6, IL-8, and CRP. In the baseline cross-sectional analysis of all 110 obese men, we observed significant associations between IIEF score and proxy indicators of elevated body fat, the vascular response to L-arginine, and circulating IL-8 and CRP levels. The association we found between IIEF score and indices of endothelial dysfunction supports the presence of common vascu-

lar pathways underlying both conditions in obese men. A disturbance in nitric oxide activity linked to reduced nitric oxide availability could provide a unifying explanation for this association. In particular, in isolated corpus cavernosum strips from patients with erectile dysfunction both neurogenic and endothelium-dependent relaxation is impaired.<sup>18</sup> Moreover, erectile dysfunction in diabetic men correlates with endothelial dysfunction and endothelial activation, including circulating concentrations of P-selectin and cellular adhesion molecules.<sup>19</sup> In addition to being a powerful indicator of risk, recent evidence suggests that CRP may directly participate in lesion formation through leukocyte activation and endothelial dysfunction.<sup>20-22</sup>

This study provides evidence that weight loss achieved by lifestyle changes can ameliorate erectile function in obese men with erectile dysfunction at baseline. In the Massachusetts Male Aging Study, Derby et al<sup>16</sup> found that men who were overweight at baseline were at an increased risk of developing erectile dysfunction regardless of whether they lost weight during follow-up. By contrast, men who initiated physical activity in midlife had a 70% reduced risk for erectile dysfunction relative to those who remained sedentary. In quantitative terms, this means that sedentary men may be able to reduce their risk of erectile dysfunction by adopting regular physical activity at a level of at least 200 kcal/d, which corresponds to walking briskly for 2 miles.<sup>23</sup> In our study, about one third of obese men with erectile dysfunction regained their sexual function after 2 years of adopting healthy behaviors, mainly regular exercise and reducing weight. This may be in line with epidemiological evidence that physical activity was associated with a 30% lower risk of erectile dysfunction, while obesity was associated with a 30% higher risk of erectile dysfunction.<sup>4</sup> Additionally, men in the intervention group showed improvement in the number of surrogate traditional and novel cardio-

vascular risk factors, which were better than those seen in men in the control group.

Obesity is a state of chronic oxidative stress and inflammation.<sup>24</sup> The increased oxidative stress associated with obesity may increase free radical formation, which could quench and deactivate nitric oxide, reducing its availability for target cells. Obese men participating in weight loss programs with dietary modifications and increased physical activity experienced reduced oxidative stress associated with improved nitric oxide availability.<sup>25</sup> As impaired nitric oxide activity appears to play an important role in the pathogenesis of erectile dysfunction,<sup>26</sup> improved nitric oxide availability associated with weight loss may be implicated in the amelioration of erectile function in our series of obese men. A reduced CRP level due to sustained lifestyle changes may have contributed to amelioration of erectile function after treatment. Levels of CRP correlate significantly with reduced nitric oxide availability<sup>22</sup> and increasing severity of penile vascular disease as measured by penile Doppler.<sup>27</sup> Moreover, consistent findings support a predictive role of CRP and IL-6 for cardiovascular events in different populations,<sup>28</sup> while IL-8 is a potent chemoattractant.<sup>29</sup>

Our study has several limitations. Psychological factors or relational situations may negatively influence erectile activity,<sup>30</sup> so it is entirely possible that improvement in mental health through alleviation of anxiety and depression in the intervention group, as well as improvement in self-image of the obese patient after weight loss, may have played a role in the results. Because the aim of the study was to assess the role of lifestyle changes on endothelial and erectile dysfunction, we did not assess psychological profiles of the participants. However, it seems unlikely that psychological factors also played an important role in the amelioration of endothelial function at the end of the study. Our findings may not be totally generalizable to primary care populations because the intervention was intensive and

involved a lot of contact with the study team. However, this should not detract from the potential importance of the findings for public health in the light of the increasing evidence that sustained lifestyle modifications have a profound impact on diseases.

Our data demonstrate that lifestyle changes, including a reduced calorie diet and increased exercise, improve erectile function in obese men and resulted in about one third of men with erectile dysfunction regaining sexual function after treatment. This improvement was associated with amelioration of both endothelial function and markers of systemic vascular inflammation. Interventions focused on modifiable health behaviors may represent a safe strategy to improve erectile function and reduce cardiovascular risk in obese patients.

**Author Contributions:** Dr Esposito had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Esposito, Giugliano.

**Acquisition of data:** Esposito, Giugliano, Di Palo, Giugliano, Marfella.

**Analysis and interpretation of data:** Esposito, D'Andrea, D'Armiendo, Giugliano.

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**Statistical expertise:** Marfella, Giugliano.

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## REFERENCES

1. Litwin MS, Nied RJ, Dhanani N. Health-related quality of life in men with erectile dysfunction. *J Gen Intern Med.* 1998;13:159-166.
2. Ventegodt S. Sex and quality of life in Denmark. *Arch Sex Behav.* 1998;27:295-307.
3. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA.* 1999;281:537-544.
4. Bacon CG, Mittleman MA, Kawachi I, et al. Sexual function in men older than 50 years of age: results from the Health Professionals Follow-up Study. *Ann Intern Med.* 2003;139:161-168.
5. Walczak MK, Lokhandwala N, Hodge MB, Guay AT. Prevalence of cardiovascular risk factors in erectile dysfunction. *J Gen Specif Med.* 2002;5:19-24.
6. Chung WS, Sohn JH, Park YY. Is obesity an un-

- derlying factor in erectile dysfunction? *Eur Urol*. 1999; 36:68-70.
7. Kopelman PG. Obesity as a medical problem. *Nature*. 2000;404:635-643.
  8. Yudkin JS, Stehouwer CDA, Emeis JJ, et al. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol*. 1999;19:972-978.
  9. Bastard J-P, Jardel C, Bruckert E, et al. Elevated levels of interleukin-6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. *J Clin Endocrinol Metab*. 2000;85:3338-3342.
  10. Ziccardi P, Nappo F, Giugliano G, et al. Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. *Circulation*. 2002; 105:804-809.
  11. Straczkowski M, Dzienis-Straczkowska S, Stepien A, et al. Plasma interleukin-8 concentrations are increased in obese subjects and related to fat mass and tumor necrosis factor- $\alpha$  system. *J Clin Endocrinol Metab*. 2002;87:4602-4606.
  12. Sullivan ME, Thompson CS, Dashwood MR, et al. Nitric oxide and penile erections: is erectile dysfunction another manifestation of vascular disease? *Cardiovasc Res*. 1999;43:658-665.
  13. Rosen RC, Riley A, Wagner G, et al. The International Index of Erectile Function (IIEF). *Urology*. 1997; 49:822-830.
  14. Nappo F, De Rosa N, Marfella R, et al. Impairment of endothelial functions by acute hyperhomocysteinemia and reversal by antioxidant vitamins. *JAMA*. 1999;281:2113-2118.
  15. Giugliano D, Marfella R, Verrazzo G, et al. L-arginine for testing endothelium-dependent vascular functions in health and disease. *Am J Physiol*. 1997; 273:E606-E612.
  16. Derby CA, Mohr BA, Goldstein I, et al. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? *Urology*. 2000;56:302-306.
  17. Vita JA, Keaney JF Jr. Exercise: toning up the endothelium? *N Engl J Med*. 2000;342:503-505.
  18. Saenz de Tejada I, Goldstein I, Azadzi K, et al. Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence. *N Engl J Med*. 1989;320:1025-1030.
  19. De Angelis L, Marfella MA, Siniscalchi M, et al. Erectile dysfunction in type II diabetes: a possible link. *Diabetologia*. 2001;44:1155-1160.
  20. Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. *Circulation*. 2000;102:2165-2168.
  21. Yeh ET, Anderson HV, Pasceri V, et al. C-reactive protein: linking inflammation to cardiovascular complications. *Circulation*. 2001;104:974-975.
  22. Verma S, Wang CH, Li SH, et al. A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. *Circulation*. 2002;106:913-919.
  23. Pate RR, Pratt M, Blair SN, et al. Physical activity and public health: a recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA*. 1995;273: 402-407.
  24. Higdon JV, Frei B. Obesity and oxidative stress: a direct link to CVD? *Arterioscler Thromb Vasc Biol*. 2003;23:365-367.
  25. Roberts C, Vaziri ND, Barnard RJ. Effect of diet and exercise intervention on blood pressure, insulin, oxidative stress, and nitric oxide availability. *Circulation*. 2002;106:2530-2532.
  26. Krane RJ, Goldstein I, Saenz de Tejada I. Impotence. *N Engl J Med*. 1989;321:1648-1659.
  27. Bank AJ, Billups KL, Kaiser DR, et al. Relation of C-reactive protein and other cardiovascular risk factors to penile vascular disease in men with erectile dysfunction. *Int J Impot Res*. 2003;15:231-236.
  28. Blake GJ, Ridker PM. Novel clinical markers of vascular wall inflammation. *Circ Res*. 2001;89:763-771.
  29. Gerszten RE, Garcia-Zepeda EA, Lim YC, et al. MCP-1 and IL-8 trigger firm adhesion of monocytes to vascular endothelium under flow conditions. *Nature*. 1999;398:718-723.
  30. Tiefer L, Schuetz-Mueller D. Psychological issues in diagnosis and treatment of erectile disorders. *Urol Clin North Am*. 1995;22:767-773.