Erectile dysfunction associates with endothelial dysfunction and raised proinflammatory cytokine levels in obese men

F. Giugliano[1], K. Esposito[2], C. Di Palo[2], M. Ciotola[2], G. Giugliano[3], R. Marfella[2], M. D'Armiento[1], and D. Giugliano[2]

[1]Chair of Urology; [2]Center for Obesity Management, Department of Geriatrics and Metabolic Diseases; [3]Chair of Plastic and Reconstructive Surgery, Second University of Naples, Naples, Italy

ABSTRACT. Erectile and endothelial dysfunction may have some shared pathways through a defect in nitric oxide activity. We evaluated associations between erectile function, endothelial function and markers of systemic vascular inflammation in 80 obese men, aged 35-55 yr, divided into two equal groups according to the presence/absence of erectile dysfunction. Compared with non-obese age-matched men [no.=50, body mass index (BMI)=24±1], obese men (all) had impaired indices of endothelial function as suggested by the reduced mean blood pressure and platelet aggregation responses to L-arginine, and higher circulating concentrations of the proinflammatory cytokines interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-18 (IL-18), as well as C-reactive protein (CRP). The mean erectile function score was 14±4 (range 7-19) in obese men with erectile dysfunction and 23.5±1 (range 22-25) in obese men without erectile dysfunction. Endothelial function showed a greater impairment in impotent obese men as compared with potent obese men. The mean blood pressure and platelet aggregation decreases following L-arginine were –1.5±1.1 mmHg and –1.1±1.2%, respectively, in obese men with erectile dysfunction, and –3.4±1.2 mmHg and –5.6±2.1%, respectively, in obese men without erectile dysfunction (p<0.01). Circulating CRP levels were significantly higher in obese men with erectile dysfunction as compared with obese men without erectile dysfunction (p<0.05). Erectile function score was positively associated with mean blood pressure responses to L-arginine and negatively associated with BMI, waist-to-hip ratio (WHR), and CRP. Erectile and endothelial dysfunction associate in obese men and may contribute to their raised cardiovascular risk through impaired nitric oxide availability elicited by a low-grade inflammatory state.
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INTRODUCTION

Erectile dysfunction is an important cause of decreased quality of life in men (1-3). The prevalence of overweight or obesity in men reporting symptoms of erectile dysfunction may be as high as 79% (4), although vascular risk factors commonly associated with obesity may play a significant role (5).

Men with a body mass index (BMI) higher than 28.7 are likely to carry a 30% higher risk for erectile dysfunction than those with a normal BMI (6). Obesity is an independent risk factor for cardiovascular disease (7). For instance, elevated levels of several proinflammatory cytokines, such as interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 18 (IL-18), as well as the sensitive marker of inflammation C-reactive protein (CRP), have been found elevated in human obesity (8-10). These vascular inflammatory markers are linked to future thrombotic events through mechanisms of plaque destabilization (11, 12). Moreover, endothelial dysfunction has been reported in obese patients and markers of low-grade inflammation are positively associated with endothelial dysfunction in human obesity (8, 13). Erectile and endothelial dysfunction may have some shared pathways through a defect in nitric oxide activity (14).

The aim of the present study was to describe associations between erectile function, endothelial func-

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Correspondence: D. Giugliano, MD, PhD, Dipartimento di Geriatria e Malattie del Metabolismo, Policlinico Universitario, Piazza L. Miraglia, 80138 Napoli, Italia.

E-mail: dario.giugliano@unina2.it

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tion and markers of systemic vascular inflammation in human obesity. For this purpose, we compared obese men with and without erectile dysfunction.

MATERIALS AND METHODS

Patients

Obese men, aged 35 to 55 yr, were recruited from the outpatient department for weight loss of the teaching hospital at the Second University of Naples, Italy. Erectile function was assessed by completing questions 1 to 5 of the International Index of Erectile Function (IIEF), which is a multidimensional questionnaire for assessing erectile dysfunction (15). The erectile function score represents the sum of questions 1 to 5 of the IIEF questionnaire, with a maximum score of 25: a score of 21 or lower indicates erectile dysfunction. All obese men were asked to complete a personal 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 h 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 mmHg), cardiovascular disease, psychiatric problems, use of drugs or alcohol abuse (at least 500 g alcohol/week in the last year), and smoking. Endocrine causes of erectile dysfunction were also excluded. Among obese subjects who satisfied exclusion criteria, 80 men (40 with and 40 without erectile dysfunction) were enrolled. Fifty non-obese men, matched for age and metabolic characteristics to the obese men, served as the control group. The study was approved by the institutional Committee of Ethical Practice of our institution, and all the study subjects gave informed written consent. Height and weight were recorded with participants wearing lightweight clothing and no shoes using a Seca 200 scale with attached stadiometer (Seca, Hamburg, Germany). BMI was calculated as weight in kg divided by the square of height in meters (kg/m^2). Waist-to-hip ratio (WHR) was calculated as waist circumference in centimeters divided by hip circumference in centimeters.

Measurements

Endothelial function was assessed with the L-arginine test, as previously described (16). Briefly after connecting men to a device for automatic measurements of blood pressure and heart rate (Finapres, Omheda 2300, Englewood, Ca, USA), an iv bolus of 3 g L-arginine (10 ml of a 30% solution of L-arginine monochloride), the natural precursor of nitric oxide, was injected within 60 sec. Blood pressure and platelet aggregation response to 1.25 micromolar adenosin diphosphate (ADP) were measured before L-arginine injection and after 10 min. L-arginine mimics some of the effects of nitric oxide, including vasodilatation and antiplatelet activity; since 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 (17). Assays for serum total and high-density lipoprotein cholesterol, triglyceride, and glucose levels were performed in the hospital's chemistry laboratory. Plasma insulin levels were assayed by radioimmunoassay (Ares, Serono, Italy). Serum samples for cytokine and CRP levels were stored at –80 C until assay. Serum concentrations of IL-6, IL-8, and IL-18 were determined in duplicate using a high-sensitive, quantitative sandwich enzyme assay (Quantikine HS, R&D Systems). High-sensitivity CRP was assayed by immunonephelometry on Behring Nephelometer 2 (Dade Behring).

Statistical analysis

Data are presented as group mean±SD unless stated otherwise. A preliminary analysis of variance (ANOVA) was used to assess the significance between groups followed by a Bonferroni post-hoc test. Parameters that were not normally distributed (cytokines and CRP) were log-transformed before analysis. Linear regression and correlation were used to evaluate relationships between variables. Multivariate regression analysis tested the independent association and contribution of BMI, WHR, indices of endothelial function, and plasma cytokine concentrations with the dependent variable (IIEF score). A value of $p<0.05$ was considered significant. All analyses were conducted using SPSS version 9.0 (SPSS Inc, Chicago, Ill).

RESULTS

Clinical and laboratory characteristics of study patients are reported in Table 1. The mean age was similar in the 3 groups; body weight and BMI were matched between the 2 obese groups, but were significantly higher than the non-obese group. Compared with non-obese men, obese men (all) had impaired indices of endothelial function as suggested by the reduced mean blood pressure and platelet aggregation responses to L-arginine. Circulating concentrations of proinflammatory cytokines and CRP were significantly higher in obese men as compared with non-obese men. Moreover, obese men had higher systolic and diastolic blood pressure, glucose, insulin and triglyceride levels, but had lower HDL-cholesterol levels than non-obese group .

Both obese groups were comparable and relatively healthy. All men had BMI values ranging from 30 to 49 kg/m^2. The mean erectile function score was 14.4±5.0 with values ranging from 7 to 19 obese men with erectile dysfunction and 23.5±1 (range 22-25) in obese men without erectile dysfunction. Endothelial function showed a greater impairment in impotent obese men as compared with potent obese men. The mean blood pressure and platelet aggregation decreases following L-arginine were –1.5±1.1 mmHg and –1.1±1.2 %, respectively, in obese men with erectile dysfunction, and –3.4±1.2 mmHg and –5.6±2.1%, respectively, in obese men without erectile dysfunction ($p<0.01$). There were no significant differences in the plasma levels of any of the cytokines evaluated between the two obese groups; however, circulating CRP levels were significantly higher in obese men with erectile dysfunction as compared with obese men without erectile dysfunction ($p<0.05$). There were no differences in any of the metabolic and hemodynamic parameters investigated between the two obese groups (Table 1).

Correlation coefficients between IIEF score and metabolic variables are shown in Table 2. Univariate correlations are given as these were little affected by adjustment for age. Erectile function score was positively correlated with mean blood pressure responses to L-arginine and negatively correlated with BMI, WHR,

Table 1 - Clinical and metabolic characteristics of the study men.*

Parameters	Obese men with erectile dysfunction (no.=40)	Obese men without erectile dysfunction (no.=40)	Non-obese men (no.=50)
Age, yr	44.5±5.1	44.0±5.0	45.1±4.8
Weight, kg	103±9.4	101±9.7	69±7.1**
BMI, kg/m^2	36.9±2.5)	36.4±2.3	24.1±1.0**
WHR	0.99±0.09)	1.0±0.09	0.84±0.7**
IIEF score	14.4±5.0	23.5±1.0°	24.0±1.0
Responses to L-arginine MBP, mmHg	–1.5±1.1	–3.4±1.2°	–6.5±1.5**
Platelet aggregation, %	–1.1±1.2	–5.6±2.1°	–13.0±4.4**
SBP, mmHg	129±7.5	128±7.7	123±6.6**
DBP, mmHg	88±3.7	87±4.1	84±3.9**
Glucose, mg/dl	103±10	104±11	95±9**
Insulin, µU/ml	20±8	19±7	9±4**
Cholesterol, mg/dl	208±32	210±29	199±28
HDL-cholesterol, mg/dl	39±10	40±9	45±8**
Triglycerides, mg/dl	163±46	168±47	126±32**
IL-6, pg/ml†	4.9 (1.9/9.5)	4.3 (2.0/8.6)	2.1 (0.3-5.2)**
IL-8, pg/ml†	5.6 (2.3/10)	5.0 (2.2/9.7)	3.1 (0.8-6.2)**
IL-18, pg/ml†	238 (180-289)	211 (167-267)	127 (50-275)**
CRP, mg/l†	4.7 (1.2/8.1)	2.9 (1.2/8.3)°	0.7 (0.2-3.2)**

*Data are presented as mean±SD or † as median (interquartile range). BMI: body mass index; WHR: waist-to-hip ratio; IIEF: International Index of Erectile Function; DPB: diastolic blood pressure; MBP: mean blood pressure; SBP: systolic blood pressure. IL-6: interleukin 6; IL-8: interleukin 8; IL-18: interleukin 18; CRP: C-reactive protein.**p<0.05 compared with obese men; °p<0.05 compared with obese men with erectile dysfunction.

and CRP. To investigate which variables might account for the association between indices of endothelial dysfunction, CRP levels, and erectile function score, multiple regression analysis was performed in which IIEF score was the dependent variable whereas BMI, WHR, indices of endothelial function, and serum CRP concentrations were the independent variables. BMI (25% of the variance, p=0.02), mean blood pressure response to L-arginine (17% of the variance, p=0.02), and CRP (18% of the variance, p=0.03) were independent predictors of IIEF score and explained nearly 60% of its variability.

DISCUSSION

In this study, we tested the hypothesis that erectile function score and indices of endothelial dysfunction associate in obese men. The physiological rationales underlying this hypothesis are that: (a) obese men may have a high prevalence of erectile dysfunction (4); (b) obesity has been positively associated with endothelial dysfunction and increased serum concentrations of vascular inflammatory markers (8, 13); and (c) both endothelial and erectile dysfunction may share some common metabolic and vascular pathway (14).

Compared with obese men without erectile dysfunction, obese men with erectile dysfunction presented a greater impairment of endothelial functions, as indicated by the more reduced blood pressure and platelet aggregation responses to L-arginine, and a greater low-grade inflammatory state, as evidenced by the higher circulating concentrations of CRP. We observed significant associations between IEEF score and proxy indicators of elevated body fat, the vascular response to L-arginine, and circulating CRP levels. The association we found between IIEF score and the indices of endothelial dysfunction supports the presence of some common vascular pathways underlying both conditions in obese men. A defective 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 (18). Moreover, erectile dysfunction in diabetic men correlates with endothelial dysfunction and endothelial activation, including circulating concentrations of p-selectin and cellular adhesion molecules (19). Lastly, in addition to being a powerful risk marker, recent

Table 2 - Correlations between the International Index of Erectile Function (IIEF) score and metabolic parameters, cytokine levels, and indices of endothelial function in obese men with erectile dysfunction (no.=40)

	IIEF score	p value
Weight	–0.40	<0.01
BMI	–0.37	<0.01
WHR	–0.35	<0.01
Glucose	–0.08	=0.15
Insulin	–0.04	=0.24
Cholesterol	–0.15	=0.08
HDL-cholesterol	0.08	=0.09
Triglycerides	–0.09	=0.12
IL-6*	–0.10	=0.06
IL-8*	–0.18	<0.05
IL-18*	–0.14	=0.08
CRP*	–0.25	<0.02
Responses to L-arginine		
Mean blood pressure	0.28	<0.025
Platelet aggregation	0.20	<0.05

*Log-transformed data. BMI: body mass index; WHR: waist-to-hip ratio; CRP: C-reactive protein; IL-6: interleukin 6; IL-8: interleukin-8; IL-18: interleukin-18. SI conversion factors: to convert glucose from mg/dl to mmol/l, multiply by 0.0555; insulin from μU/ml to pmol/l, multiply by 7.175; TC and HDL-C from mg/dl, to mmol/l, multiply by 0.0259; and triglycerides from mg/dl to mmol/l, multiply by 0.0113.

evidence suggests that CRP may directly participate in lesion formation through leukocyte activation and endothelial dysfunction (20, 21). CPR, at concentrations known to predict diverse vascular insults, profoundly quenches nitric oxide synthesis, while augmenting the release of endothelin-1 and up-regulating adhesion molecules and chemoattractant chemokines, uncovering a proinflammatory and proatherosclerotic phenotype (22).

Obesity is a state of chronic oxidative stress and inflammation, as inflammation is a source of oxidative stress and many inflammatory indices, including CRP and proinflammatory cytokines, are elevated in obesity (23). In particular, in the Framingham Offspring Cohort Keaney et al. (24) found that increased urinary excretions of the F_2-isoprostane 8-epiPGF$_{2\alpha}$ were positively associated with BMI. In addition to serve as biomarker of oxidative stress, F_2-isoprostanes exert vascular effects, such as vasoconstriction (25). 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. As impaired nitric oxide activity appears to play an important role in the pathogenesis of erectile dysfunction (26), reduction of body weight may in theory improve NO availability. For instance, obese men on weight loss programs with dietary modifications and increased physical activity experienced reduced oxidative stress associated with improved NO availability (27). Moreover, reduced CRP levels associated with sustained lifestyle changes may contribute to amelioration of erectile function, as CRP levels correlate significantly with reduced NO availability (22) and increasing severity of penile vascular disease as measured by penile Doppler (28).

The vascular inflammatory markers herein evaluated (CRP, IL-6, and IL-18) are linked to future thrombotic events through mechanisms of plaque destabilization (11, 12), while IL-8 is a potent chemoattractant and may be responsible for the recruitment of neutrophils and T lymphocytes into the subendothelial space, for adhesion of monocytes to endothelium, and for migration of vascular smooth muscle cells (29).

In conclusion, erectile and endothelial dysfunction associate in obese men and may contribute to their raised cardiovascular risk through impaired nitric oxide availability elicited by a low-grade inflammatory state. As several modifiable lifestyle factors, including physical activity and leanness, are associated with maintenance of good erectile function in men (30), and lifestyle changes reduce the inflammatory state of the obese patient (31), interventions should focus on modifiable health behaviors to maintain erectile function, including reducing weight and increasing physical activity.

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