



2nd AME Italian Meeting

Associazione Medici Endocrinologi

Joint Meeting with AACE

American Association of Clinical Endocrinologists



Reggio Emilia, Italy - November 8-10, 2002

Clinical Symposium

Therapeutic Options in Obesity

Chairman

Antonino Cartabellotta (Palermo, Italy)

Participants

Francesco Giorgino (Bari, Italy)

Richard Dickey (Winston-Salem, NC, USA)

Clinical scenario (1)

- CN is a 54 yrs old obese housewife, with hypertension and recent history of snoring, dyspnea and palpitations.
- Referred episodes of binge eating.

Clinical scenario (2)

Personal history

- Non-smoker
- 2 pregnancies (2 sons) and surgical menopause at age 50 (uterine leiomyomas)
- Obesity since age 33
- Hypertension since age 40, treated with ramipril (5 mg/die), furosemide (25 mg/die), and amlodipine (10 mg/die)
- No history of peptic ulcer disease or gastritis

Family history

- Mother with type 2 diabetes, obesity, hypertension and CHD/MI
- Father with obesity

Clinical scenario (3)

Physical examination

- 126 kg
- 165 cm
- BMI 46.3
- Waist 122 cm
- WHR 1.07
- BP 140/90 mmHg, on anti-hypertensive drugs

Clinical scenario (4)

Laboratory findings

- Blood glucose 107 mg/dL
- Fasting serum insulin 34 mU/L
- Impaired glucose tolerance at OGTT
- Lipid profile:
 - Triglyceride 260 mg/dL
 - Total cholesterol 190 mg/dL
 - HDL cholesterol 33 mg/dL
- Normal liver, thyroid and kidney function.
- Blood low-normal pO_2 , normal pCO_2 , normal CBC.

Clinical scenario (5)

- **Echocardiogram:** Mild LVH, LVEF 40%.
- **Actual calorie intake**
 - Difficult to assess due to binge eating episodes (approximately 2,800 kCal/day).
 - Estimated basal energy expenditure: 1,883 kCal/day
 - Activity level: low (activity factor: 1.3)
 - Estimated total energy expenditure: 2,448 kCal/day
- **Binge Eating Scale:** highly positive score.

Diagnosis

**Class III obesity in subject with IGT,
hypertriglyceridemia, hypertension,
and binge eating disorder**

CLINICAL QUESTIONS



1. What is your first choice to obtain weight loss?

1. Drug therapy
2. Low-calorie diet
3. Very-low calorie diet
4. Exercise program
5. 2 + 4
6. 1 + 3

Therapeutic decision

We prescribe a low-calorie diet (1,700 kCal/day; 55% CHO, 20% protein, 25% lipid)

Main sources of pre-appraised evidence

Practice guidelines

- 2001 - Prodigy (UK NHS)
- 1999 - Canadian Task Force on Preventive Health Care
- 1998 - National Heart, Lung, and Blood Institute, North American Association for the Study of Obesity (NHLBI-AASO)
- 1998 - American Association of Clinical Endocrinologists, American College of Endocrinology (AAACE-ACE)

NIH vs AACE-ACE guidelines

Guideline Content Comparison

- NIH provides explicit reasoning behind their judgments in evidence tables, ranking the level of evidence for each major recommendation; AACE/ACE offers literature citations to support their major recommendations.
- AACE/ACE discusses topics that are not covered by NIH, including the prevention of obesity, the role of physician counseling, and obesity in adolescents and children

National Guideline Clearinghouse (NGC).

Guideline synthesis: Assessment and treatment of overweight and obesity.

NIH vs AACE-ACE guidelines

Areas of difference

- NIH does not endorse severe caloric restriction (very low calorie diets or VLCDs); whereas, AACE/ACE countenance their use under special circumstances.
- AACE/ACE permit a wider range of pharmaceutical options; whereas, NIH favors weight loss drugs that have received FDA approval for long-term use, following testing for at least 1 year.
- Similarly, AACE/ACE comment on surgical options that the NIH does not consider.

National Guideline Clearinghouse (NGC).

Guideline synthesis: Assessment and treatment of overweight and obesity.

Main sources of pre-appraised evidence

Evidence-compendia

- Clinical Evidence. Issue 7 (July, 2002)

Technology assessment reports

- 2002 - SBU
- 2002 - NICE
- 2000 - ASERNIP-S

*National Heart, Lung, and Blood Institute,
North American Association for the Study of Obesity*

**The practical guide.
Identification, evaluation,
and treatment of overweight
and obesity in adults**

Bethesda, Md, 1998

- 1- Controlled energy diets (LCDs) are recommended for weight loss in overweight and obese persons (Evidence Category A).
- 2- Reducing fat as part of a LCD is a practical way to reduce calories. (Evidence Category A).
- 3- Reducing dietary fat alone without reducing energy intake is not sufficient for weight loss.
- 4- A diet that is individually planned to help create a deficit of 500-1000 kcal/d should be an integral part of any program aimed at achieving a weight loss of 0.45 to 0.90 kg/wk (Evidence Category A).

NHLBI, NAASO. 1998

*American Association of Clinical Endocrinologists
American College of Endocrinology*

**AACE/ACE position statement
on the prevention, diagnosis
and treatment of obesity**

1997 (revised 1998)

Table 5
General Criteria for Selecting a Weight-Management Strategy*

Basic treatment with LCD	Basic treatment with LCD or VLCD[†]	Basic treatment with LCD or VLCD[†] and pharmacotherapy	Surgical treatment
BMI ≥ 25 Good diet history	BMI ≥ 35 BMI ≥ 30 with comorbid conditions Poor diet history	BMI ≥ 35 BMI ≥ 30 [†] BMI 27-29 with comorbid conditions [‡] Poor diet history	BMI > 40 BMI ≥ 35 with life-threatening or disabling comorbid condition(s) Obesity history ≥ 5 yr No history of alcoholism or major psychiatric disorders ≥ 18 yr old

*BMI = body mass index; LCD = low-calorie diet; VLCD = very-low-calorie diet.

[†]VLCDs are reserved for nonelderly adults with high health risk due solely to BMI or BMI with serious comorbid condition(s).

[‡]In combination with LCD only.

CLINICAL QUESTIONS



2. Do you prescribe a cognitive-behavioral therapy?

1. Yes
2. No

Therapeutic decision

- Cognitive-behavioral therapy plus self-help groups

What evidence about
behavioral therapy?

Shaw K, Kenardy J, O'Rourke P, Del Mar C.

Psychological interventions for obesity (Protocol for a Cochrane Review)

*In: The Cochrane Library, Issue 4, 2002.
Oxford: Update Software.*

What evidence about behavioral therapy?

- 22 RCTs strongly indicate that behavioral strategies, to reinforce diet and physical activity, produce weight loss in the range of 10% over a period of 4-12 months (no additional benefits are found at 3 to 5 years)
- No one behavior therapy appeared superior to any other in its effect on weight loss.
- Multimodal strategies appear to work best and interventions with the greatest intensity appear to be associated with the greatest weight loss.

What recommendations about behavioral therapy?

- Behavior therapy is a useful adjunct when incorporated into treatment for weight loss and weight maintenance (Evidence Category B).
- Weight loss and weight maintenance therapy should use the combination of controlled energy diets, increased physical activity, and behavioral therapy (Evidence Category A).

Why not drugs?

Why not drugs?

- A combined intervention of behavioral therapy, a controlled-energy diet and increased physical activity provides the most successful therapy for weight loss and weight maintenance.
- This type of intervention should be maintained for at least 6 months before considering pharmacotherapy.

NHLBI, NAASO. 1998

Why not drugs?

- AACE and ACE do not “condone” antiobesity agent therapy when used simply for cosmetic purposes or when weight loss can be achieved and maintained without pharmacotherapy.
- Although antiobesity agents can improve weight loss, they may also be associated with adverse effects, including even the potential for a fatal outcome.

Clinical Evidence

Categorization of obesity drug treatments in adults

Beneficial

None

Likely to be beneficial

None

Trade-off between benefits and harms

Sibutramine, Phentermine, Mazindol, Orlistat

Clinical Evidence

Categorization of obesity drug treatments in adults

Unknown effectiveness

Diethylpropion, Fluoxetine, Sibutramine plus Orlistat

Unlikely to be beneficial

None

Likely to be ineffective or harmful

Phenylpropanolamine, Fenfluramine, Dexfenfluramine,
Fenfluramine plus phentermine

Clinical Evidence. July, 2002

CLINICAL QUESTIONS



3. How to treat IGT and hypertriglyceridemia

1. Drug therapy
2. Non-drug therapy

Therapeutic decision

- Non-drug therapy

What evidence about ↓ of serum lipids?

- There is strong evidence from 14 RCTs that weight loss produced by lifestyle modifications is accompanied by reductions in serum triglyceride levels, total cholesterol and LDL-C levels, and by increases in HDL-C levels.
- There is suggestive evidence from the 8 pharmacotherapy RCTs that weight loss produced by drugs and adjuvant lifestyle modifications, including energy restriction and physical activity, does not result in consistent effects on blood lipid levels.

NHLBI, NAASO. 1998

What recommendations about ↓ of serum lipids?

- Weight loss is recommended to lower levels of total cholesterol, LDL-C, and triglycerides, and to raise low levels of HDL-C in overweight and obese persons with dyslipidemia (Evidence Category A).

NHLBI, NAASO. 1998

What evidence about ↓ of blood glucose?

- There is strong evidence from the 9 RCTs that weight loss produced by lifestyle modification reduces blood glucose levels in overweight and obese persons without diabetes
- There is suggestive evidence from RCTs that weight loss induced by drugs does not appear to improve blood glucose levels any better than weight loss through lifestyle therapy in overweight persons, both with and without type 2 diabetes.

What recommendations about ↓ of blood glucose?

- Weight loss is recommended to lower elevated blood glucose levels in overweight and obese persons with type 2 diabetes (Evidence Category A).

NHLBI, NAASO. 1998

Clinical Scenario (6)

1st control visit (at week 4)

- Reduced frequency of binge eating episodes

	Baseline	Week 4
Weight	126	122
BMI	46.3	44.8
Waist	122	117
WHR	1.07	0.97
TG	260	-
BP	140/90	115/75

Therapeutic decision

- We reduce anti-hypertensive drugs:
 - 5 mg ramipril PO once daily
 - 25 mg furosemide PO alt. dieb.
 - suspend amlodipine
- We maintain the same therapy for obesity

Clinical Scenario (7)

2nd control visit (at week 12)

- No binge eating episodes

	Baseline	Week 4	Week 12
Weight	126	122	116
BMI	46.3	44.8	42.6
Waist	122	117	117
WHR	1.07	0.97	0.97
TG	260	-	160
BP	140/90	115/75	105/60

Therapeutic decision

- 5 mg ramipril PO once daily
- Cognitive-behavioral therapy plus self-help groups
- We apply a modest reduction in calorie intake (1,500 kCal/day)
- We prescribe a 30-min walking session daily

What evidence about
physical exercise?

Shaw K, Del Mar C, O'Rourke P, Tito F

Exercise for obesity
(Protocol for a Cochrane Review)

*In: The Cochrane Library, Issue 4, 2002.
Oxford: Update Software.*

What recommendations about physical exercise?

1- Physical activity should be an integral part of weight loss therapy: initially, moderate levels of physical activity for 30 to 45 minutes, 3 to 5 days a week, should be encouraged.

2- All adults should set a long term goal to accumulate at least 30 minutes of moderate intensity physical activity on most, and preferably all, days of the week (Evidence Category B).

3-The combination of a reduced energy diet and increased physical activity is recommended because it produces weight loss that may also result in decreases in abdominal fat and increases in cardiorespiratory fitness. (Evidence Category A).

NHLBI, NAASO. 1998

What recommendations about physical exercise?

- Although regular, moderate physical activity alone results in a limited weight loss, it is an essential and high-priority element of any weight-management program.

AACE/ACE. 1998

Clinical Scenario (8)

3rd control visit (at week 24)

- Referred improvement of snoring, and palpitations.
- Patient is capable of performing mild physical activity.
- Referred dyspnea with moderate exercise.
- Binge Eating Scale: negative score.
- ECG: LVH.
- Echocardiogram: LVEF 50%.

3rd control visit (at week 24)

	Baseline	Week 4	Week 12	Week 24
Weight	126	122	116	110
BMI	46.3	44.8	42.6	40.4
Waist	122	117	117	114
WHR	1.07	0.97	0.97	0.95
BP	140/90	115/75	105/60	110/75
TG	260	-	160	130
Blood glucose	107	-	-	97
OGTT	IGT	-	-	Normal
Serum insulin	34	-	-	22

CLINICAL QUESTIONS



4. More than diet, physical activity, and psychological support, what is your therapeutic choice to further decrease and maintain weight?

1. None
2. Very Low Calorie Diet
3. Pharmacotherapy
4. Obesity surgery

Therapeutic decision

- Laparoscopic adjustable silicone gastric band
- Cognitive-behavioral therapy plus self-help groups
- Low-calorie diet (gradually increased to 1,400 kCal/day)
- 30-min walking session daily
- 5 mg ramipril PO once daily

CLINICAL QUESTIONS



5. Do you think appropriate the obesity surgery?

1. Yes

2. No

OBESITY SURGERY

What recommendations from
clinical practice guidelines?

*National Heart, Lung, and Blood Institute,
North American Association for the Study of Obesity*

**The practical guide:
identification, evaluation,
and treatment of overweight
and obesity in adults**

Bethesda, Md, 1998

- Surgery is one option for weight reduction in a limited number of patients with clinically severe obesity (BMI \geq 40 or BMI \geq 35 with comorbid conditions).
- Should be reserved for patients in whom efforts at medical therapy have failed and who are suffering from the complications of extreme obesity.

*American Association of Clinical Endocrinologists
American College of Endocrinology*

**AACE/ACE position statement
on the prevention, diagnosis
and treatment of obesity**

1997 (revised 1998)

- Surgical treatment of obesity must be considered carefully because serious complications can occur.
- It may be considered only in carefully selected patients who meet the following criteria:
 - Very high medical risk: BMI >40 or BMI 35-39 with life-threatening or disabling conditions such as diabetes mellitus, dyslipidemia, hypertension, or serious cardiopulmonary disorders
 - Obesity has been present for at least 5 years
 - No history of alcoholism or major psychiatric disorder
 - Age 18-65 years

Swedish Council on Technology Assessment in Health Care

Obesity
Problems and Interventions
A Systematic Review

June, 2002

- Surgical treatment may be appropriate for severely obese individuals, but only after other treatment attempts have failed.
- BMI >40 is generally accepted as a cutoff point for surgery (in special cases, at a lower degree of obesity)
- Surgical interventions gives substantial gains in health and quality of life, but carries some risk for complications and, in isolated cases, death.

NICE - National Institute for Clinical Excellence

Technology Appraisal No. 46

**Guidance on the use of
surgery to aid weight reduction
for people with morbid obesity**

July, 2002

Surgery is recommended if all of the following criteria are fulfilled:

- people who have been receiving intensive management in a specialised hospital obesity clinic
- individuals should be aged 18 years or over
- evidence that all appropriate and available nonsurgical measures have been adequately tried but have failed to maintain weight loss
- no specific clinical or psychological contraindications
- individuals should be generally fit for anaesthesia and surgery
- individuals should understand the need for long-term follow-up.

- Given the uncertainty surrounding the evidence for the relative safety and effectiveness of different surgical interventions, it is not possible to distinguish between them on grounds of cost-effectiveness.
- The choice of surgical intervention should therefore be made jointly by the individual and the clinician after considering the best available evidence, the facilities and equipment available, and the experience of the surgeon who would perform the operation.

ASERNIP-S
Australian Safety and Efficacy
Register of New Interventional Procedures-Surgical

ASERNIP-S Report N° 9

**Laparoscopic adjustable
gastric banding for the
treatment of obesity**

April, 2000

RESULTS (1)

- There was little high level evidence available and few comparative studies.
- **Safety**
 - Mortality rates were less than 1 in 1000, which is less than that quoted in many reviews of other surgical procedures for the treatment of obesity.
 - Likewise, morbidity rates did not appear to exceed those quoted for other procedures.

RESULTS (2)

- **Efficacy**

- Most operations appear to be completed in under 2 hours.
- Most studies reported rates of conversion to open procedures of under 4%.
- Patients appear to be discharged earlier than those undergoing vertical banded gastroplasty, and also appear to become more mobile and independent after surgery, although initially positive responses to the surgery tend to diminish with time.

RESULTS (3)

- **Efficacy**

- The laparoscopic adjustable gastric band appears capable of producing substantial weight loss up to 4 years

- Longer term data has not been published and the consistency of weight loss across the patient population is also unclear due to poor reporting of variance in most studies.

CONCLUSION AND RECOMMENDATIONS

- The safety and/or efficacy of procedure cannot be determined at the present time due to an incomplete and/or poor quality evidence-base.
- It is recommended that further research be conducted to establish safety and/or efficacy.

Clinical Scenario (9)

4th control visit (at week 48)

- Referred marked improvement of dyspnea.
- Patient is able to perform moderate physical activity.

4th control visit (at week 48)

	Baseline	Week 12	Week 24	Week 48
Weight	126	116	110	95
BMI	46.3	42.6	40.4	34.8
Waist	122	117	114	100
WHR	1.07	0.97	0.95	0.86
BP	140/90	105/60	110/75	120/80
TG	260	160	130	105
Blood glucose	107	-	97	94
OGTT	IGT	-	Normal	Normal
Serum insulin	34	-	22	18