Obesity and Its Impact on the Gastrointestinal Tract

Grand Rounds

By: Amy Tiu

Objectives: Highlight the Impact of Obesity

- Esophageal Disease
- Irritable Bowel Syndrome
- Biliary Disease
- Gastrointestinal Cancer
- Liver and Pancreatic Transplant
- Inflammatory Bowel Disease
- Brief overview of Orlistat

Case

- 28 yo female presents with burning and epigastric pain for one year
- Reports started after the birth of her first child
- 5 feet 2 inches
- 220 pounds

Case: What is her BMI?

- Weight (kg)/ Ht (meters squared)
- Body Mass Index
- The patient's BMI = 40.2

Body Mass Index

	Good Weights							Increasing Risk													
	BMI																				
Height	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
4′10″	91	96	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167	172	177	181	186	191
4′11″	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173	178	183	188	193	198
5′	97	102	107	112	118	123	128	133	138	143	148	153	158	163	168	174	179	184	189	194	199	204
5′1″	100	106	111	116	122	127	132	137	143	148	153	158	164	169	174	180	185	190	195	201	206	211
5′2″	104	109	115	120	126	131	136	142	147	153	158	164	169	175	180	186	191	196	202	207	213	218
5′3″	107	113	118	124	130	135	141	146	152	158	163	169	175	180	186	191	197	203	208	214	220	225
5′4″	110	116	122	128	134	140	145	151	157	163	169	174	180	186	192	197	204	209	215	221	227	232
5′5″	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204	210	216	222	228	234	240
5′6″	118	124	130	136	142	148	155	161	167	173	179	186	192	198	204	210	216	223	229	235	241	247
5′7″	121	127	134	140	146	153	159	166	172	178	185	191	198	204	211	217	223	230	236	242	249	255
5′8″	125	131	138	144	151	158	164	171	177	184	190	197	203	210	216	223	230	236	243	249	256	262
5′9″	128	135	142	149	155	162	169	176	182	189	196	203	209	216	223	230	236	243	250	257	263	270
5′10″	132	139	146	153	160	167	174	181	188	195	202	209	216	222	229	236	243	250	257	264	271	278
5′11″	136	143	150	157	165	172	179	186	193	200	208	215	222	229	236	243	250	257	265	272	279	286
6′″	140	147	154	162	169	177	184	191	199	206	213	221	228	235	242	250	258	265	272	279	287	294
6′1″	144	151	159	166	174	182	189	197	204	212	219	227	235	242	250	257	265	272	280	288	295	302
6′2″	148	155	163	171	179	186	194	202	210	218	225	233	241	249	256	264	272	280	287	295	303	311
6′3″	152	160	168	176	184	192	200	208	216	224	232	240	248	256	264	272	279	287	295	303	311	319
6′4″	156	164	172	180	189	197	205	213	221	230	238	246	254	263	271	279	287	295	304	312	320	328

Case: Why is she obese? Is it what she ate?

- No regular exercise
- No regular diet
- 582 kcal 38.7 grams of fat

BMI-associated Disease Risk

	Obesity Class	BMI (kg/m^2)	Risk
Underweight		< 18.5	Increased
Normal		18.5 - 24.9	Normal
Overweight		25.0 - 29.9	Increased
Obesity	I	30.0 – 34.9	High
	II	35.0 – 39.9	Very High
	III	≥ 40.0	Extremely High

Additional risks: (1) waist circumference > 40 inches in men and >35 inches in women; (2) weight gain of > 5 kg since age 18-20 years; (3) poor aerobic fitness; and (4) Southeast Asian descent.

Clinical guidelines on the Identification, Evaluation, and Treatment of Overweight And Obesity in Adults- The Evidence Report. Obesity Research, 1998. 6 (supplement 2 51S-209S.

Gastroesophageal Reflux Disease (GERD)

- Relationship with obesity still not clear, but most studies find a strong association
- In the U.S., accepted as an independent risk factor for the presence of GERD
- Obesity is a risk factor that can identify patients with GERD who are at greatest risk for developing gastroesophageal junction adenocarcinoma

Gastroesophageal Reflux Disease (GERD)

- A study of 65,363 adults in Sweden, found that obese subjects had a 3.5 fold increased risk of heartburn (independent of age, gender, and smoking $p<0.001$)

Nilson, M., et al. Obesity and estrogen as risk factors for gastroesophageal Reflux symptoms. JAMA, 2003. 290(1): 66-72

Manometric abnormalities in the morbidly obese

Condition	No. of patients (%)
Defective LES	10 (16%)
Hypertensive LES	11 (18%)
Diffuse esophageal spasm	2 (3%)
Nutcracker esophagus	3 (5%)
Ineffective esophageal disorder	1 (2%)
Nonspecific esophageal disorder	14 (23%)

Esophageal motility

- Conflicting data
- A three year study of 111 morbidly obese patients demonstrated no correlation with BMI and lower esophageal sphincter pressure

Jaffin, B. et al. High prevalence of asymptomatic esophageal motility disorders Among morbidly obese patients, 1999.9(4): 390-5

Esophageal Motility

	Obese (BMI=44)	Control (BMI=22)
Lower Esophageal Sphincter Pressure (mmHg)	11.9 +/- 5.3	15.9 +/- 2.7

Iovino, P. Abnormal esophageal acid exposure is common in morbidly obese patients and improves after a successful Lap-band system implantation Surg Endosc, 2002.16(11): p 1631-5

Why is there conflicting data for obesity and gastroesophageal disease?

- Symptoms may not reflect abnormalities
- Symptoms may be functional, null of any objective findings
- Patient who are obese may have a tendency to deny symptoms as part of behavioral tendencies toward eating despite discomfort

Obesity and Irritable Bowel Syndrome

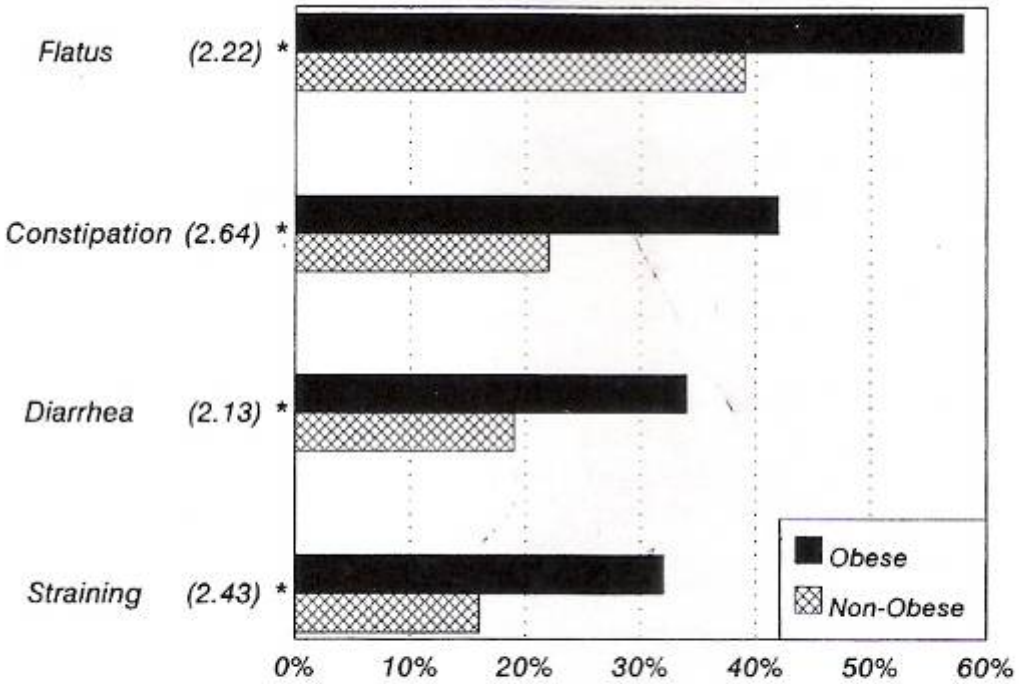


FIG. 3. The prevalence of gastrointestinal symptoms associated with obesity collapsed over binge groups. The relative risk of each symptom is shown in parentheses. The asterisk (*) represents a significant χ^2 statistic at the 0.05 level.

Crowell, M. et al. Prevalence of gastrointestinal symptoms in obese and normal Weight binge eaters. Am J Gastroenterol, 1994. 89(3): 387-91

Obesity and Irritable Bowel Syndrome

- Fifty-eight twin pairs discordant for symptoms associated with irritable bowel syndrome (IBS) were evaluated.
- Significant association between IBS and obesity (OR=2.6; CI 1.0-6.4)
- May represent a familial-environmental influence on IBS

Svedberg, P. Extraintestinal manifestations assoicated with irritable bowel syndrome: a twin study.Aliment Pharmacol Ther,2002. 16(5):975-83

Obesity and Irritable Bowel Syndrome

- Etiology of the association with obesity unclear
- In 1994, Crowell et al. examined gastrointestinal symptoms in obese, obese binge eaters, normal, and normal obese binge eaters

Obesity and Irritable Bowel Syndrome

- Obesity was associated with more frequent constipation, diarrhea, straining, and flatus, whether or not subjects reported binge eating
- Indigestion was more prevalent in both obese groups

Crowell, M. et al. Prevalence of gastrointestinal symptoms in obese and normal Weight binge eaters. Am J Gastroenterol, 1994. 89(3): 387-91

What if you are obese and binge eat?

- First, binge eating has been defined by the Eating Disorders Work Group and DSM-IV
  - Eating in a discrete period of time an amount of the definitely larger than most
  - A sense of lack of control over eating during the episode
  - At least 3 of behavioral indicators

What if you are obese and binge eat?

- Binge eating has been defined by the Eating Disorders Work Group and DSM-IV

  (continued)

  - Marked distress regarding the binge
  - Two episodes a week for 6 months
  - Person does not fit criteria for bulimia nervosa or does not abuse medications

What if you are obese and binge eat?

FIG. 1. The average number (mean ± SE) of upper and lower gastrointestinal symptoms reported by each group. The asterisk (*) indicates significance at the $p < 0.05$ level.

Obesity and Gastrointestinal Tract Symptoms

- In a cohort study in Australia (n=777), a regression model adjusting for sex, education, smoking, alcohol and all gastrointestinal symptoms, older age, less early satiety, increased stool frequency, and heartburn were all independently associated with increasing BMI (all $p<0.01$)

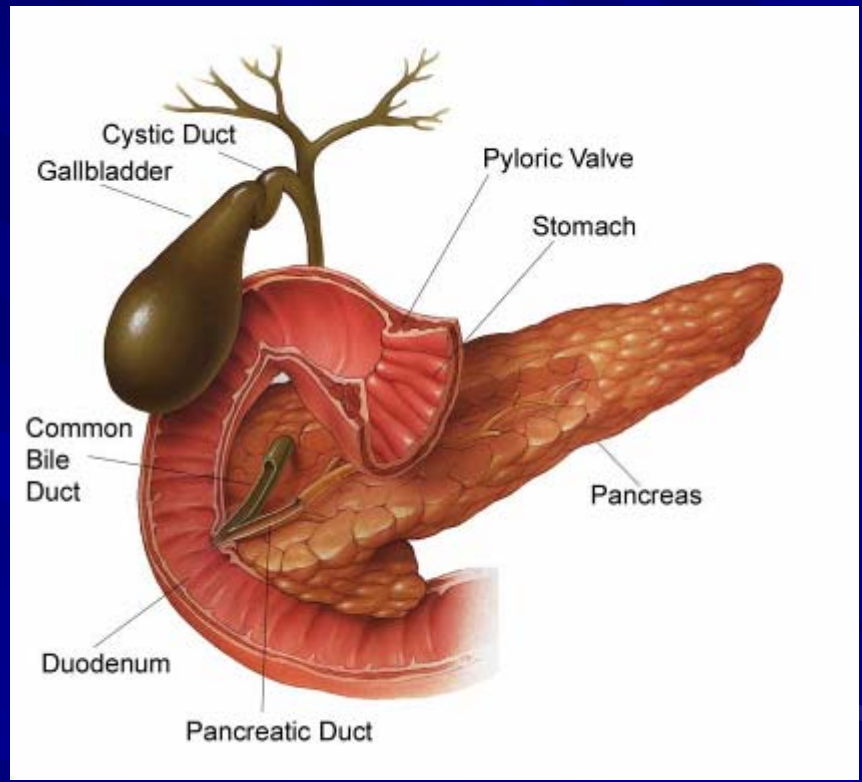
Talley, N.J., et al. Association of upper and lower gastrointestinal tract symptoms with Body mass index in an Australian cohort. Neurogastroenterol. Motil, 2004. 16(4):413-9

Obesity, IBS, & GI symptoms

- Evidence of an association between obesity and IBS
- Evidence that obesity associated with chronic gastrointestinal symptoms that may not fit definition of IBS but affect daily life of patients

Obesity and Biliary Disease

- Sixty percent of morbidly obese individuals undergoing gastric bypass surgery have gallbladder pathology



Seinige, U.et al. Gallbladder disease In the morbidly obese patient. Obes Surg 1991;1:51-56

Obesity and cholelithiasis

- The Nurses Health Study demonstrated that, compared to lean women, obese women had a two-fold excess risk of symptomatic gallstones; and extremely obese women had a seven-fold excess risk of symptomatic gallstones.

Stampfer, M., et al Risk of symptomatic gallstones in women with severe Obesity. Am J Clin Nutr, 1992. 55(3): 652-8

Obesity and cholelithiasis

- Ten year follow-up of men in the Health Professionals study found an increased risk of cholelithiasis with severity of overweight.

Field, A. et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. Arch Intern Med. 2001.161(13):1581-6

Obesity and Biliary disease

- Risk of developing cholelithiasis increases with BMI in both genders
- Unfortunately, risk of developing gallstones increases with weight loss
- Risk factors for new formation of cholelithiasis include
  - Weight loss rate 1.5 kg per week
  - Very low calorie diet with no fat content

Risk of new gallstones

Intervention	Risk
Low calorie diet for 8 to 16 weeks	10-12%
Gastric bypass Within 12-18 months Post –op	>30%

One third of these stones formed were found to be asymptomatic

Erlinger, S., Gallstones in obesity and weight loss. Eur J Gastroenterol Heptol 2000.12 (12) 1347-52

Mechanisms for increased cholelithiasis after rapid weight loss

- Bile lithogenicity increases by decreased synthesis of bile acids and impaired gallbladder motility because of inadequate fat stimulation
- This may also be combined with increased gallbladder secretion of mucin and calcium, as well as increased E2 prostaglandins and arachidonic acid

Festi, D. et al. Gallbladder motility and gallstone formation in obese patients Following very low calorie diets. Use it (fat) to lose it (well). Int J Obes Relat Metab Disord, 1998.22(6):592-600

Prevention of Cholelithiasis in an obese patient trying to lose weight

- During rapid weight loss from a very low calorie diet with a high fat composition (577 kcal with 12 gm of fat) for 6 months; the high fat intake could prevent gallstone formation, probably by maintaining an adequate gallbladder emptying, which could counterbalance lithogenic mechanisms during weight loss.

Festi, D. et al. Gallbladder motility and gallstone formation in obese patients Following very low calorie diets. Use it (fat) to lose it (well). Int J Obes Relat Metab Disord, 1998.22(6):592-600

Rough example of 577 kcal and 12 grams of fat

1 plain chick fil a sandwich

(410 kcal and 16 gm fat)

1 regular Coca cola

(140 kcal and 0 gm fat)

0.25 piece of a Pilsbury cookie

Prevention of Cholelithiasis in an obese patient trying to lose weight

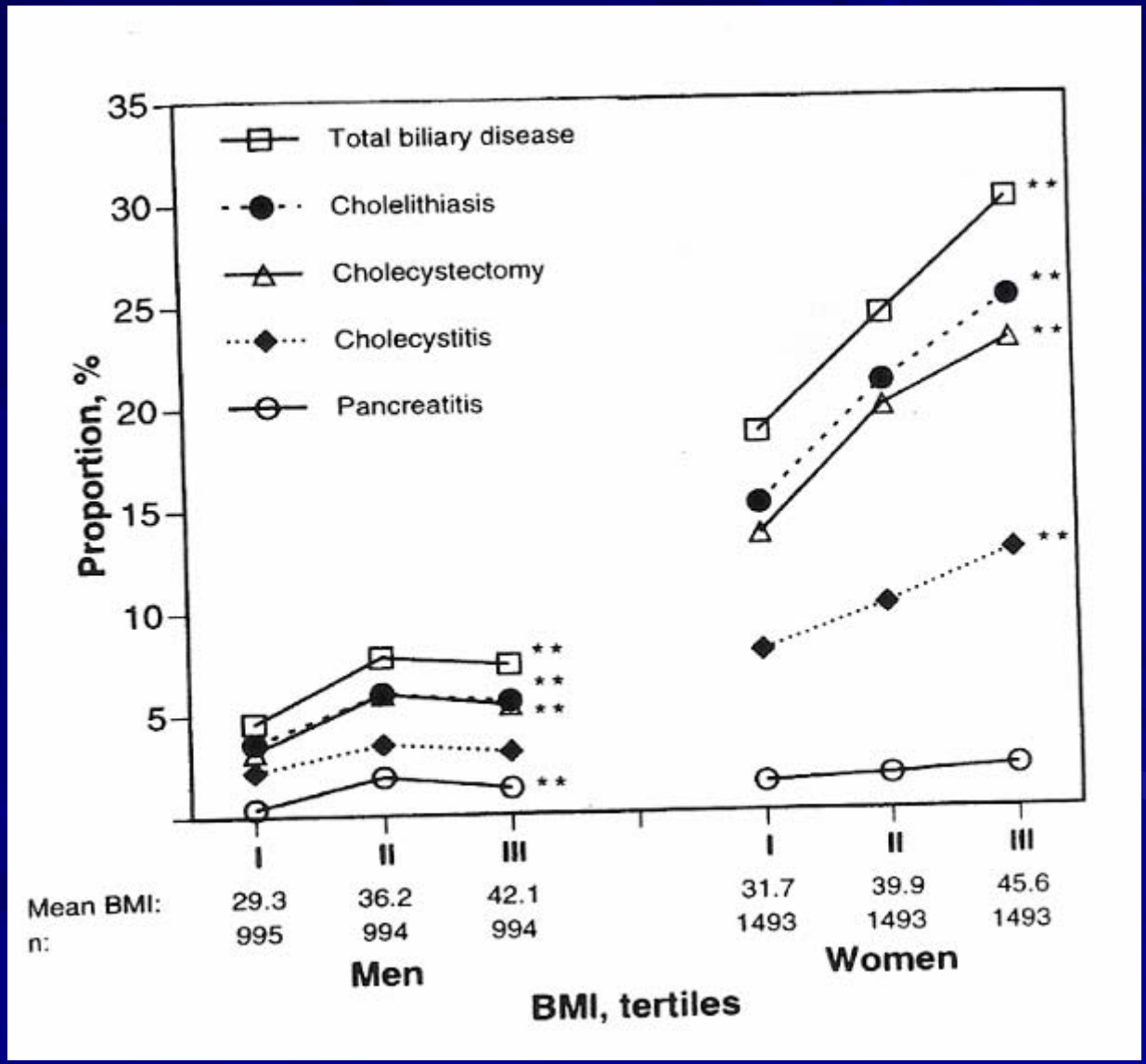
- Increasing physical activity lowers biliary cholesterol levels and reduces gallstone disease in obese individuals.

Chuang, C. et al. Physical activity, biliary lipids, and gallstones in obese subjects. Am J of Gastroenterol 2001;96:1860-1865

- Orlistat added to a hypocaloric diet may protect overweight individuals from developing gallstones when they diet.

Trouillot, T.E. et al. Orlistat maintains biliary lipid composition and heptobiliary function in obese subjects undergoing moderate weight loss. Am J Gastroenterol 2001;96:1888-94

Obesity and Biliary disease



Torgerson et al

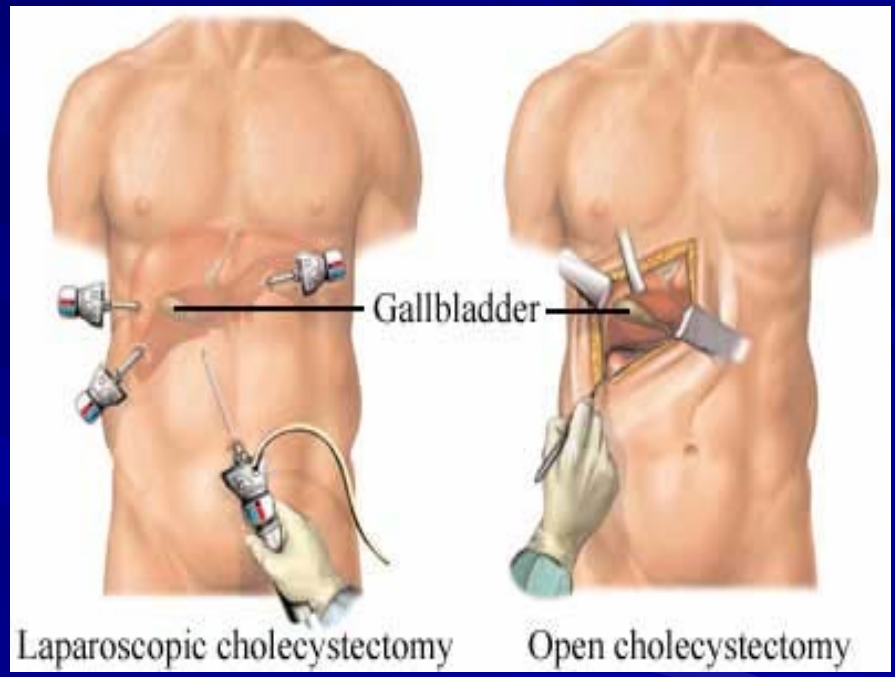
Obesity and Biliary disease

- In a study of 6328 obese patients and 1125 randomly selected reference individuals, there was an increased prevalence of gallstones, gallbladder disease, and pancreatitis in the obese.

Torgerson, J.S., et al., Gallstones, gallbladder disease, and pancreatitis: Cross sectional and 2-year data from the Swedish Obese Subjects (SOS) And SOS reference studies. Am J Gastroenterol, 2003.98 (5):1032-41

Obesity and Biliary disease

- Obesity has also been found to be a significant preoperative predictor of conversion to laparotomy in patients undergoing laparoscopic cholecystectomy. In some cases the trocars and instruments are too short.



Fried, G. et al. Factors determining
Conversion to lapartomy in patients
Undergoing laparoscopic cholecystectomy
Am J Surg, 1994.167(1):35-9

Obesity and Pancreatitis

	Number (%)		
	Nonobese (BMI < 30) (N = 294)	*Obese (BMI ≥ 30) (N = 26)*	P
Respiratory failure	28 (9.5)	3 (11.5)	0.73
Patients with systemic complications	74 (25.2)	10 (38.5)	0.21
Patients with local complications	82 (27.9)	18 (69.2)	<0.0001
Patients with organ failures	43 (14.6)	4 (15.4)	1.0
Mortality in patients with organ failures	22 (51.1)	2 (50)	1.0
Total mortality	22 (7.5)	2 (7.7)	1.0
Ranson score			
<3	206 (65)	15 (57.7)	
3–5	80 (24.1)	9 (34.6)	0.48
≥6	34 (10.9)	2 (7.7)	

Association of Severe Pancreatitis, Complications, Ranson Signs, and Outcome in Obese and Nonobese Patients
From: TSAI: Dig Dis Sci, Volume 43(10).October 1998.2251-2254

Obesity and pancreatitis

- Regardless of cause, obesity increased severity of acute pancreatitis
- 9-13 times more likely if high waist to hip ratio or waist circumference
- Risk of peri-pancreatic/pancreatic necrosis increased 3 fold

Mery, C. et al., Android fat distribution as a predictor of severity in acute pancreatitis Pancreatology. 2002;2:543-549

Obesity and Gastrointestinal Cancer

The proportion of all deaths from cancer that is attributable to overweight and obesity in the United States adults 50 years of age or older may be as high as 14 percent in men and 20 percent in women

Obesity and Cancer

Under the assumption that the relationship with obesity and cancer causal, more than **90,000** deaths per year from cancer might be avoided if everyone in the adult population could maintain a body mass index of under 25 throughout life.

Calle, E. et al., Overweight, obesity, and mortality from cancer in a prospectively Studied cohort of U.S. adults. N Engl J Med 2003.348 (17):1625-38

Esophageal and Gastric Cancer

- Increased risk of adenocarcinoma of esophagus by factor of 2-3 with increased body mass index (BMI)
- Increased risk of adenocarcinoma of gastric cardia especially in men
- Why? Reason unclear

Gallbladder Cancer

- Elevated risk for gallbladder cancer in women with increased BMI (>40) by a factor of two

- Why? Most likely associated with increased risk of cholelithiasis

Obesity and Pancreatic Cancer

- An established risk factor for pancreatic cancer
- Meta-analysis of 14 studies involving 6000 cases of pancreatic cancer estimated that the relative risk of developing pancreatic cancer was about 20% greater in patients with a BMI>30 compared to normal weight individuals.

Berrington de Gonzalez, A., et al. A meta-analysis of obesity and the risk of Pancreatic cancer. Br J Cancer. 2003.89(3):519-23

Obesity and Pancreatic Cancer

- Why? One suggested mechanism includes the notion that increased adiposity increases insulin resistance and hyperplasia of pancreatic beta cells. Perhaps also leading to expansion of other pancreatic cell populations leading to cancer

Obesity and Hepatic Cancer

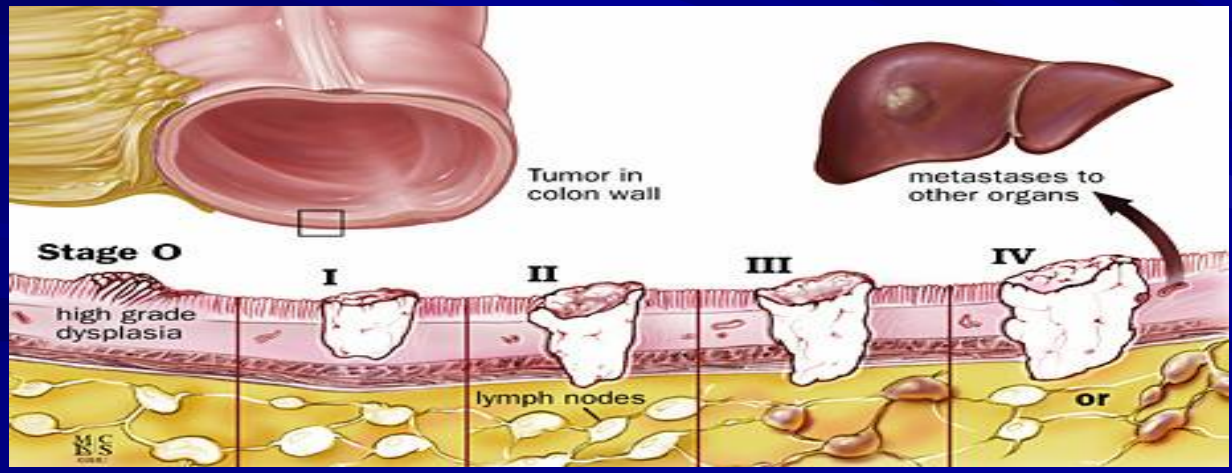
- Increased risk of hepatocellular cancer (HCC); May be again due to affects of adiposity leading to cirrhosis
- Increased risk of HCC-related mortality; Obese men have a five fold increased risk compared to men with normal BMI and HCC

Adami, HO et al. Obesity and mortality from cancer.

N Engl J Med 2003;348:1623-1624.

Obesity and Colon Cancer

- Being overweight increases the incidence and lethality of colon cancer
- Why? Mechanism unclear



Obesity and Colon Cancer

- In a study of 13,420 men and women who had participated in the First National Health and Nutrition Examination Survey, twenty-year follow-up demonstrated that the hazard ratio for colon cancer increased with BMI, and is 3-4 fold higher in obese individuals than in those with a normal BMI

Ford, E., Body mass index and colon cancer in a national sample of adult US men And women. Am J Epidemiol, 1999.1509(4).390-8

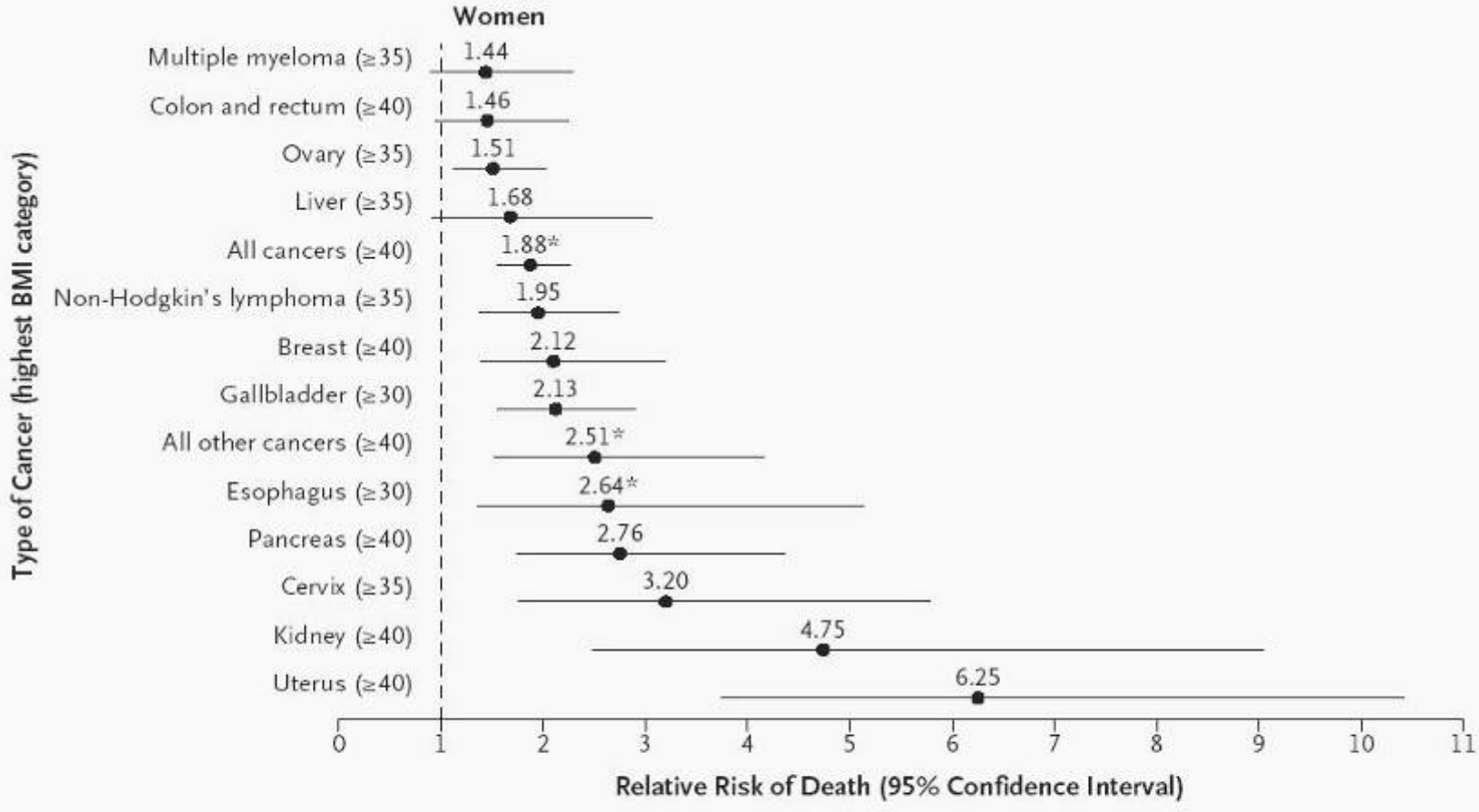


Figure 2. Summary of Mortality from Cancer According to Body-Mass Index for U.S. Women in the Cancer Prevention Study II, 1982 through 1998.

For each relative risk, the comparison was between women in the highest body-mass-index (BMI) category (indicated in parentheses) and women in the reference category (body-mass index, 18.5 to 24.9). Asterisks indicate relative risks for women who never smoked. Results of the linear test for trend were significant ($P \leq 0.05$) for all cancer sites.

Calle, E. et al., Overweight, obesity, and mortality from cancer in a prospectively Studied cohort of U.S. adults. N Engl J Med 2003.348 (17):1625-38

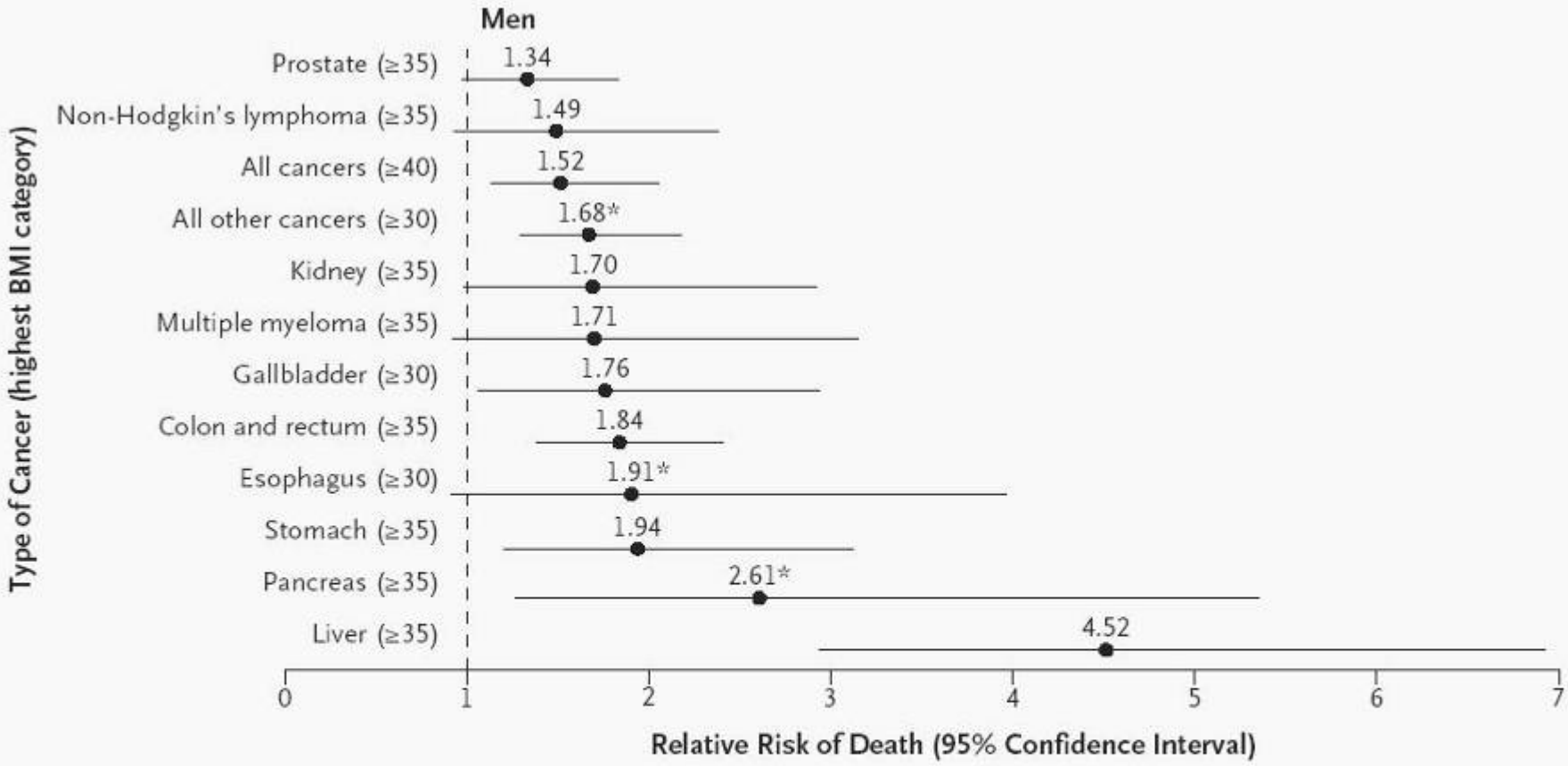


Figure 1. Summary of Mortality from Cancer According to Body-Mass Index for U.S. Men in the Cancer Prevention Study II, 1982 through 1998.

For each relative risk, the comparison was between men in the highest body-mass-index (BMI) category (indicated in parentheses) and men in the reference category (body-mass index, 18.5 to 24.9). Asterisks indicate relative risks for men who never smoked. Results of the linear test for trend were significant ($P \leq 0.05$) for all cancer sites.

Calle, E. et al., Overweight, obesity, and mortality from cancer in a prospectively Studied cohort of U.S. adults. N Engl J Med 2003.348 (17):1625-38

Obesity and GI organ transplant

Obesity and Liver transplant

- Recipient obesity is a significant risk factor for decreased graft survival after almost all types of abdominal organ transplants.

- Following liver transplantation in severely obese patients, there was a higher rate of wound infection and death attributed to multi-organ failure compared to patients with a BMI<35

Sawyer, R. et al. Increased early morbidity and mortality with acceptable long-term Function in severely obese patients undergoing liver transplantation. Clin Transplant 1999. 13(1 Pt 2):126-30

Obesity and Liver transplant

- In liver transplants, donor obesity is associated with steatosis of the graft, which in turn is associated with a higher incidence of primary nonfunction

Obesity and Pancreatic transplant

- Donor obesity also impacts outcomes
- 711 cadaver pancreas transplants were analyzed for outcomes
- BMI > 30 donor group, surgical infections and thrombosis were significantly higher
- Exact reason unclear, may be increased fat around pancreas and increased vascular disease in donor

Humar, A., et al. The impact of donor obesity on outcomes after cadaver pancreas Transplants. Am J Transplant, 2004 4(4): 605-10

Obesity and IBD

- 2065 obese and non-obese Crohn's patients were studied
- Time of development of anoperineal abscess or fistula was shorter in obese patients
- Obese patients were more prone to develop an active disease requiring hospitalization

Blain, A. et al., Crohn's disease clinical course and severity in obese patients. Clin Nutr, 2002. 21 (1):51-7

Obesity and IBD

- Obesity not a risk factor for Crohn's
- Use of steroids not more frequent in obese patients
- Minority of Crohn's patients obese

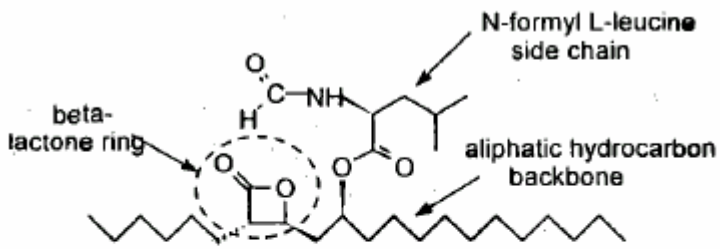
Anti-obesity medications: Using the GI tract

Anti-obesity medications approved

Drug	Sibutramine	Orlistat
Trade names	Meridia (US) Reductile (Europe)	Xenical
Dosage	5–15 mg once daily	mg three times daily before meals
DEA schedule	Class IV	Not scheduled
Mechanism	Reuptake inhibitor of serotonin and norepinephrine; promotes satiety; reducing food intake; mildly thermogenic	Pancreatic lipase inhibitor; blocks absorption of 30% of fat in intestine
Lifestyle requirement	Greatest efficacy is with structure meal plan that includes portion control	Diet should be consistent in 30% of energy content as fat; high fat indiscretions must be avoided
Cautions	Blood pressure and pulse elevations may occur and patients should be monitored; should not be used with MAOIs; not recommended for use in patients with heart disease	Patients must be counseled regarding steatorrhea with high fat meals; vitamin supplement required

What is Orlistat?

- Trade name: Xenical by Roche
- Chemical name: tetrahydrolipstatin
- FDA approved in 1999
- Dose 120 mg PO TID
- Cost approx $139.00 each month

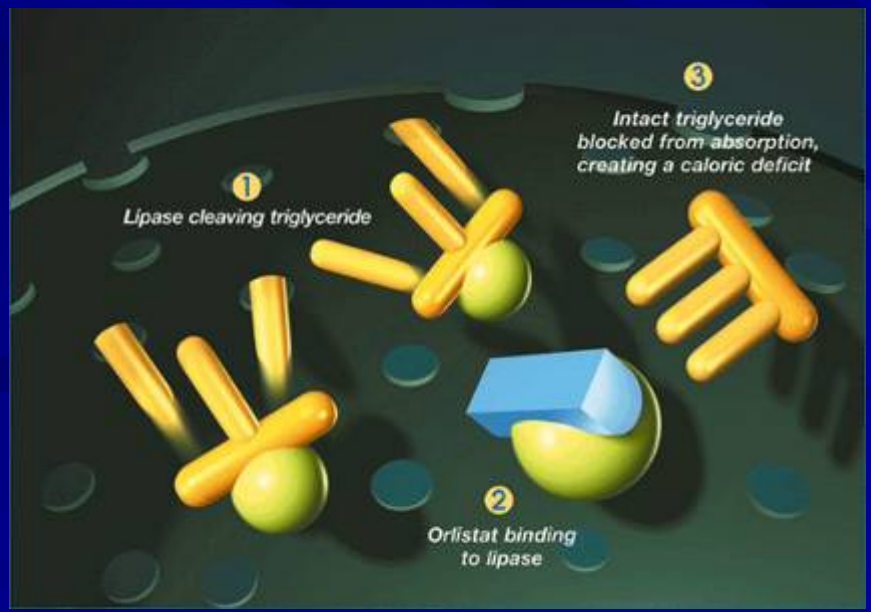


$C_{29}H_{53}NO_5 = 495.74$

[2*S*-[2α(*R**),3β]]-*N*-formyl-L-leucine 1-[(3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl ester

How does Orlistat work?

- Inhibits fat digestion by blocking the enzymatic action of pancreatic lipase
- Dose-dependent inhibitor
- Decreases intestinal triglyceride hydrolysis



How does Orlistat work?

- Inactivates gastric and pancreatic lipase by forming a covalent bond with the serine residue site
- This leaves triglycerides undigested causing a steatorrheal diarrhea
- Recommended to work best when given with diet that has approximately 30% fat content

What is a diet that is 30% fat?

- Patient 62 inches 110 lbs; BEE = 1200
- 30% kcal from fat would be 360 kcal
- 40 grams of fat each day

300 kcal 12 grams fat

126 kcal 2.7 grams

More examples of 40 grams of fat

14

20

25

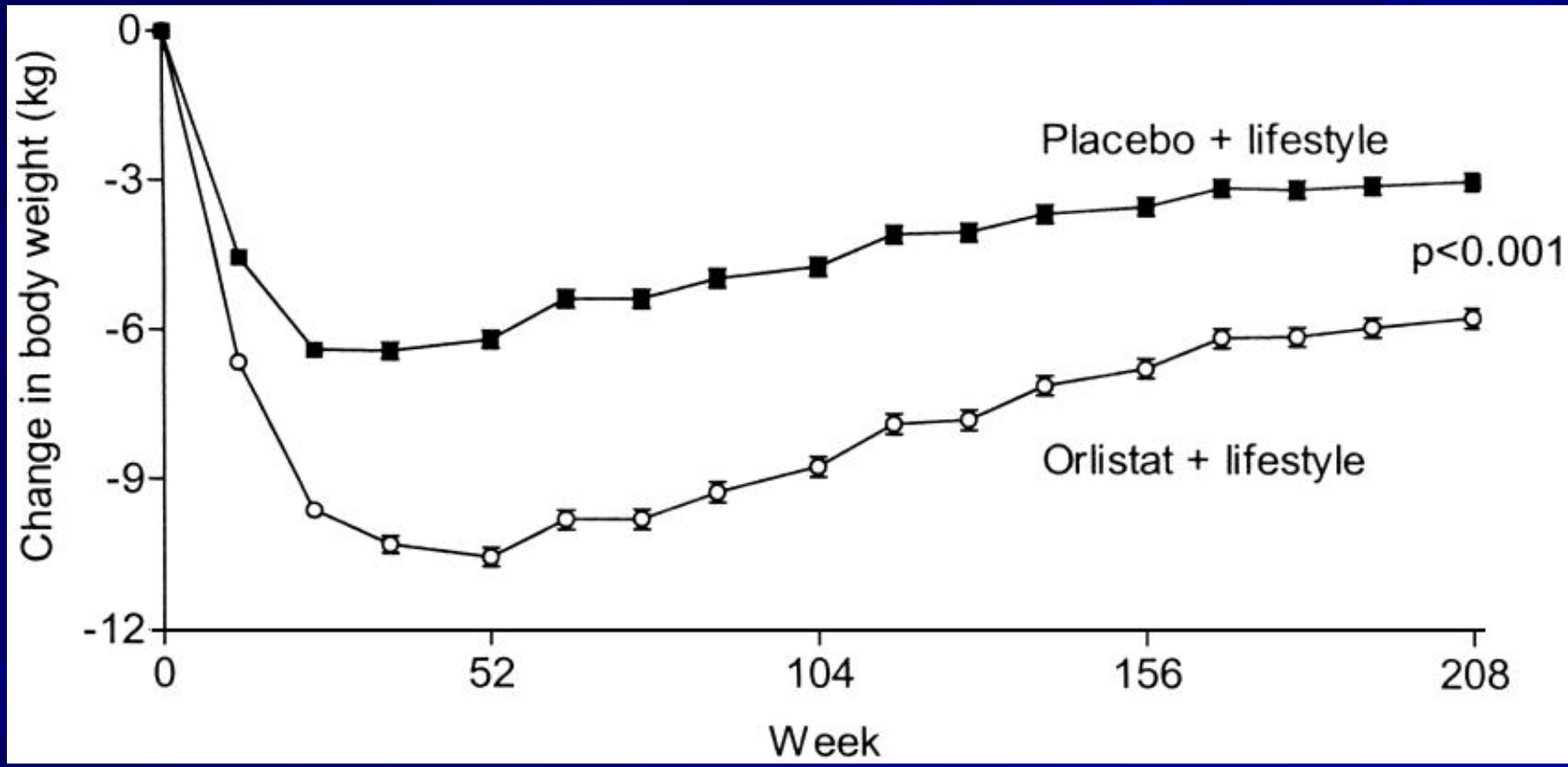
Adverse reactions

- Deficiency of fat-soluble vitamins can occur especially vitamin D. Recommended that patient take a multivitamin

- Side effects: oily, spotty flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation, and fecal incontinence (most commonly seen from a meta-analysis of nine clinical trials)

Padwal, R. et al. Long-term pharmacotherapy for obesity and overweight. Cochrane Database Syst Rev 2003;:CD004094

Orlistat compared to Placebo



Weight loss (means ± SEM) during 4 years of treatment with orlistat plus lifestyle changes or placebo plus lifestyle changes in obese patients (LOCF data).

From: Torgerson: Diabetes Care, Volume 27(1).January 2004.155-161

Orlistat

- In a review of 28 Randomized Clinical trials, it was shown to improve weight loss and improve serum lipid profiles
- Total cholesterol, HDL, and LDL were improved

Hulton B. et al. Changes in body weight and serum lipid profiles in obese patients treated with orlistat in addition to a hypocaloric diet: a systematic review of randomized clinical trials. Am J Clin Nutr 2004:80 (6): 1461-8

XENDOS study

- Xenical in the prevention of diabetes in obese subjects
- 4 year double-blind randomized, placebo controlled prospective study carried out in 22 Swedish medical centers between 1997-2002
- 3,305 patients
- Lifestyle changes plus either orlistat 120 mg TID or placebo

XENDOS study

- After 4 years, the cumulative incidence of diabetes was 9.0% placebo and 6.2% with orlistat (risk reduction 37.3% p=0.0032)
- Mean weight loss was greater with orlistat (5.8 kg vs 3.0 kg with placebo) p<0.001

Torgerson, J et al. Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study. Diabetes Care 2004; 27:155-161.

Note Orlistat is NOT Olestra

- Orlistat is drug
- Olestra is a food additive
- Non absorbable fat substitute introduced in 1996
- Only approved for use in snack products by FDA

Future in Obesity treatment

Target	Delivery	Trial
NPY antagonist	Intranasal (Pfizer)	Clinical trial
Hypothalamus (Rimonanbant)	*PO Acomplia (Sanofi-Aventis)*	Phase III
PYY	Intranasal (Merck)	Phase I
GLP-1	IV (Amylin)	Phase III
CCK	Oral	Phase II

Korner et al. Pharmacological Approaches to Weight Reduction 2004;JCEM 89(6):2616-2621

Summary

- Obesity increases GI diseases
- While most research has focused on its effects in the fields of cardiology and endocrinology, growing knowledge has been directed to the gut and its important role in contributing, managing, and eradicating obesity
- Growing research into using the gut as a target for treatment