Bariatric medicine treating obesity and more

Dr. Ole Schmiedel MRCP MD RFACP

Physician& Endocrinologist

Service Clinical Director Auckland Diabetes Centre, Greenlane

Learning aims:

- Case based discussion
- 'Severe and complex' obesity = medical condition / disease
- Obesity and associated complication & medical problems 'hidden' behind obesity (don't miss...)
- How to do an individualized, comprehensive medical work-up and management (medications)
- Assessment pearls

Case 1

PMHx:

- 64 female (ref from GP 03/2018)
- Weight 148kg, BMI 43kg/m2
- Edmonton Obesity Score 3
- Type 2 diabetes for 4 years (MAU, no DR, significant neuropathic leg pain)
- Urinary incontinence (? Prolapse)
- HBP, Dyslipidemia, OSA on CPAP, GERD due to reflux, Vit. D deficiency, VV surgery, no NAFLD
- Mild ankle edema and dyspnea on walking >500m, balance problems, worse last 6/12
- 1 child IVF, amenorrhea and possible PCOS (never confirmed)
- Mild depression

CC:

- Referred for weight management assessment
- Anemia with possible pr bleeding
- Back and abdominal pain, peripheral neuropathy

<u>FHx:</u>

 Mother obese, father IHD and DM, siblings heavy

Weight and eating behaviors:

- Early onset weight gain age 12
- frequent cycling
- never lost weight for longer than 6/12
- emotional eating and comfort eating
- cravings for chocolate and sweets
- eats before going to bed and finds it very difficult to deal with cravings
- Previous problems with stopping smoking

' referred for bariatric surgery, however, she told me that she was concerned about the procedure and wanted to find alternative ways of dealing with her weight' Complications: The Edmonton Obesity Staging System (EOSS) for Assessing RISK



Sharma AM et al. Int J Obes. 2009

EOSS: EDMONTON OBESITY STAGING SYSTEM - Staging Tool

STAGE 0

- NO sign of obesity-related risk factors
- NO physical symptoms
- NO psychological symptoms
- NO functional limitations

Case Example:

Physically active female with a BMI of 32 kg/m², no risk factors, no physical symptoms, no self-esteem issues, and no functional limitations.



WHO Obesity Classfication

STAGE 1

- Patient has obesity-related SUBCLINICAL risk factors (borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc.) - OR -
- MILD physical symptoms patient currently not requiring medical treatment for comorbidities

(dyspnea on moderate exertion, occasional aches/pains, fatigue, etc.) - OR -

 MILD obesity-related psychological symptoms and/or mild impairment of well-being (quality of life not impacted)

Case Example:

38 year old female with a BMI of 59.2 kg/m², borderline hypertension, mild lower back pain, and knee pain. Patient does not require any medical intervention.

Class III, Stage 1 Obesity

WHO CLASSIFICATION OF WEIGHT STATUS (BMI kg/m²)

Obese Class I 30 - 34.9 Obese Class II 35 - 39.9 Obese Class III≥40

Stage 0 / Stage 1 Obesity



Patient does not meet clinical criteria for admission at this time. Please refer to primary care for further preventative treatment options.

STAGE 2

 Patient has ESTABLISHED obesity-related comorbidities requiring medical intervention (HTN, Type 2 Diabetes, sleep apnea, PCOS, osteoarthritis, reflux disease) - OR - MODERATE obesity-related psychological symptoms (depression, eating disorders, anxiety disorder) - OR -MODERATE functional limitations in daily activities

(quality of life is beginning to be impacted)

Case Example:

32 year old male with a BMI of 36 kg/m² who has primary hypertension and obstructive sleep apnea.

Class II, Stage 2 Obesity





STAGE 3

- Patient has significant obesity-related end-organ damage (myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis) - OR -
- SIGNIFICANT obesity-related psychological symptoms (major depression, suicide ideation) - OR -
- SIGNIFICANT functional limitations
- (eg: unable to work or complete routine activities, reduced mobility)
- SIGNIFICANT impairment of well-being (quality of life is significantly impacted)

Case Example:

49 year old female with a BMI of 67 kg/m² diagnosed with sleep apnea, CV disease, GERD, and suffered from stroke. Patient's mobility is significantly limited due to osteoarthritis and gout.

Class III, Stage 3 Obesity

STAGE 4

- SEVERE (potential end stage) from obesity-related comorbidities - OR -
- SEVERELY disabling psychological symptoms OR -
- SEVERE functional limitations

Case Example:

45 year old female with a BMI of 54 kg/m² who is in a wheel chair because of disabling arthritis, severe hyperpnea, and anxiety disorder.

Class III, Stage 4 Obesity

Edmonton Staging System Can Predict Mortality Better than BMI



Padwal R et al. CMAJ. 2011

Case 1 – cont.

Medication

- Metformin 1g bd
- Gliclazide 80mg bd
- Metoprolol CR 190mg OD
- Losartan 50mg OD
- Amlodipine 10mg OD
- Omeprazole 40mg OD
- Atorvastatin 40mg nightly
- Paroxetine 20mg
- Allopurinol 12mg OD
- Amitriptyline 50mg nocte
- Trimethoprim 300mg od

Examination:

- Acanthosis noted, thyroid normal
- No discolored striae
- Significant ankle swelling (non-pitting edema)
 lymphedema rather than cardiac failure
- CV unremarkable, JVP not visible
- Lungs clear
- No abdominal masses, tender suprapubic area
- BP 150/95mmHg
- Significant peripheral neuropathy (more radiculopathy than glove and stocking distribution)

Which medication is *the odd one out* – **not** causing weight gain?

- 1. Atenolol
- 2. Sulphonylureas
- 3. Pioglitazone
- 4. Estrogens
- 5. Gabapentin
- 6. Amitriptyline
- 7. Bupropion
- 8. Paroxetine
- 9. Antihistamines
- 10. Sodium valproate



Clinical Practice Guideline

Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline

Caroline M. Apovian, Louis J. Aronne, Daniel H. Bessesen, Marie E. McDonnell, M. Hassan Murad, Uberto Pagotto, Donna H. Ryan, and Christopher D. Still

Boston University School of Medicine and Boston Medical Center (C.M.A.), Boston, Massachusetts 02118; Weill-Cornell Medical College (L.J.A.), New York, New York 10065; Denver Health Medical Center (D.H.B.), Denver, Colorado 80204; Brigham and Women's Hospital (M.E.M.), Boston, Massachusetts 02115; Mayo Clinic, Division of Preventative Medicine (M.H.M.), Rochester, Minnesota 55905; Alma Mater University of Bologna (U.P.), S. Orsola-Malpighi Hospital Endocrinology Unit, 40138 Bologna, Italy; Pennington Biomedical Research Center (D.H.R.), Baton Rouge, Louisiana 70808; and Geisinger Health Care System (C.D.S.), Danville, Pennsylvania 17822

Objective: To formulate clinical practice guidelines for the pharmacological management of obesity.

Conclusions:

- 1. Medications for **chronic** weight management can be useful adjuncts
- 2. Many medications for diabetes, depression, and chronic diseases have weight effects
- 3. Knowledgeable prescribing can aid in the prevention and management of obesity and improve health

Case 1 – cont.

Medication

- Metformin 1g bd
- Gliclazide 80mg bd
- Metoprolol CR 190mg OD
- Losartan 50mg OD
- Amlodipine 10mg OD
- Omeprazole 40mg OD
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- Significant peripheral neuropathy (more radiculopathy than glove and stocking distribution)

Questions:

- 1. What's the *medical* diagnosis and what are the differentials?
- 2. What about weight management (medications, diet, exercise)
- 3. Is medical weight management realistic?
- 4. How would you approach it?

Questions:

 What's the medical diagnosis and what are the differentials?



- Obesity EOSS
- Obesity associated
 - Metabolic
 - Mechanical
 - Emotional /social
- GIM
 - Differential diagnosis for neuropathy
 - P/V or PR bleeding



Questions:

What about weight management (medications, diet, exercise)

- 1. Guidelines (UK, US, Europe, NZ)
- 2. Individualized and tailored approach
- 3. Very detailed assessment
- 4. All aspects included
- 5. Start with dietary
 - 1. used VLCD with meal replacements (lean data)
- 6. Exercise
 - 1. based on what is possible and sustainable
 - 2. person has done in the past (walking)
- 7. Medical:
 - 1. Physicians approach
 - 2. Make a medical diagnosis or DD if appropriate
 - 3. Adjustment of medications
 - 4. Start weight management medication (choice, timing, titration)
- 8. Psychological support if appropriate
- 9. Follow up and ongoing support

Questions:

3. Is medical weight management realistic?

- 1. What are we aiming for?
 - 1. How much?
 - 2. For how long?
- 2. Weight loss with different modalities
 - 1. With VLCD
 - 2. With different medications
 - 3. Combined approaches
 - 4. With BS

Questions:

- 1. How would you approach it?
- What happened ?– the second part of the story

- 1. VLCD started with dietitian
- 2. Initial weight loss
- 3. Ongoing medical concerns
- 4. The Dx and referrals
- 5. The current situation and outlook

Information from the patients folder

- Weight 148kg 132kg with VLCD and medication adjustment
- HbA1c 56 mmol/mol
- MRI spine bony lesion compressing spinal canal at L2/3 neurogenic claudication – excise the lesion
- Assessed for OSA CPAP started June 2018
- Postmenopausal bleeding hysteroscopy and polypectomy
- Regained some weight to 136kg (stable)
- Preparing for her operation

Primary care-led weight management for remission of type 2 $\rightarrow \mathcal{W}$ is \mathcal{Q} diabetes (DiRECT): an open-label, cluster-randomised trial

Michael EJ Lean*, Wilma S Leslie, Alison C Barnes, Naomi Brosnahan, George Thom, Louise McCombie, Carl Peters, Sviatlana Zhyzhneuskaya, Ahmad Al-Mrabeh, Kieren G Hollingsworth, Angela M Rodrigues, Lucia Rehackova, Ashley J Adamson, Falko F Sniehotta, John C Mathers, Hazel M Ross, Yvonne McIlvenna, Renae Stefanetti, Michael Trenell, Paul Welsh, Sharon Kean, Ian Ford, Alex McConnachie, Naveed Sattar, Roy Taylor*

Summary

Background Type 2 diabetes is a chronic disorder that requires lifelong treatment. We aimed to assess whether intensive weight management within routine primary care would achieve remission of type 2 diabetes.

Published Online December 5, 2017 http://dx.doi.org/10.1016/

Methods:

- open-label, cluster-randomized trial, 49 primary care practices in Scotland and the Tyneside region of England.
- wide range of social and geographic features
- Eligible participants were aged 20–65 years
- type 2 diabetes within the previous 6 years, and had a body-mass index (BMI) of 27–45 kg/m2.
- (The inclusion criteria were revised to specify that the most recent HbA1c value should be greater than 6.0% (>43 mmol/mol) and, if less than 6.5% (<48 mmol/mol), individuals should still be receiving antidiabetic medication.)
- A nurse or dietitian provided the intervention (VLCD) using Counterweight-Plus weight management
- All oral antidiabetic and antihypertensive drugs were discontinued on day 1 (reintroduced if indicated by regular monitoring of blood glucose and blood pressure)

	Intervention group (n=149)	Control group (n=149)			
Sex					
Female	66 (44%)	56 (38%)			
Male	83 (56%)	93 (62%)			
White ethnicity	146 (98%)	147 (99%)			
Age (years)	52.9 (7.6)	55·9 (7·3)			
Weight (kg)	101.0 (16.7)	98.8 (16.1)			
Body-mass index (kg/m²)	35·1 (4·5)	34-2 (4-3)			
Waist (cm)	107.5 (8.4)	106-5 (8-9)			
Systolic blood pressure (mm Hg)	132.7 (17.5)	137-2 (16-0)			
Diastolic blood pressure (mm Hg)	84.6 (10.2)	85.5 (8.8)			
Time since diabetes diagnosis (years)					
Mean (SD)	3.0 (1.7)	3.0 (1.8)			
Median (range)	3.1 (0.0-6.0)	2.6 (0.2-6.0)			
HbA _{1c}					
%	7.7 (1.25)	7.5 (1.05)			
mmol/mol	60 (13·7)	58 (11.5)			
Fasting glucose (mmol/L)	9.22 (3.29)	8.82 (2.54)			
Prescribed oral antidiabetic medication	111 (74·5)	115 (77-2)			
Number of oral antidiabetic medications					
0	38 (26%)	34 (23%)			
1	65 (44%)	79 (53%)			
≥2	46 (31%)	36 (24%)			



Figure 2: Primary outcomes and remission of diabetes in relation to weight loss at 12 months

(A) First co-primary outcome: achievement of at least 15 kg weight loss at 12 months. (B) Second co-primary outcome: remission of diabetes (glycated haemoglobin <6.5% [48mmol/mol], off antidiabetic medication for 2 months). (C) Remission of diabetes, in relation to weight loss achieved at 12 months (both groups combined).



Figure 3: Change in weight of participants who remained in the trial and those who dropped out during each phase of the intervention Error bars represent 95% CIs.

Newer Antiobesity Medications

Agent	Mechanism of Action	Approval Date
Lorcaserin ^a	 Selective serotonin receptor agonist (5-HT_{2C}) 	2012
Phentermine/ Topiramate ER ^b	 Sympathomimetic Anticonvulsant (GABA receptor modulator, carbonic anhydrase inhibitor, glutamate antagonist) 	2012
Naltrexone SR/ Bupropion SR ^c	 Opioid receptor antagonist Dopamine/noradrenaline reuptake inhibitor 	09/10/2014
Liraglutide 3.0 mg ^d	 GLP-1 receptor agonist 	12/23/2014

a. Belviq[®] PI 2012.^[12] b. Qsymia[®] PI 2014^[9]; c. CONTRAVE[®] PI^[10]; d. Saxenda[®] PI.^[11]

Sustainability – need appropriate long-term planning and management

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Persistence of Hormonal Adaptations to Weight Loss

Priya Sumithran, M.B., B.S., Luke A. Prendergast, Ph.D., Elizabeth Delbridge, Ph.D., Katrina Purcell, B.Sc., Arthur Shulkes, Sc.D., Adamandia Kriketos, Ph.D., and Joseph Proietto, M.B., B.S., Ph.D.

Conclusions

- One year after initial weight reduction, levels of the circulating mediators of appetite that encourage weight regain after diet-induced weight loss do **not** revert to the levels recorded before weight loss
- Long-term strategies to counteract this change may be needed to prevent obesity relapse



Figure 3. Mean (±SE) Fasting and Postprandial Ratings of Hunger and Desire to Eat at Baseline, 10 Weeks, and 62 Weeks.

Ratings were based on a visual-analogue scale ranging from 0 to 100 mm. Higher numbers indicate greater hunger or desire.

N Engl J Med 2011;365:1597-604. Copyright © 2011 Massachusetts Medical Society.



Figure 2. Mean (±SE) Fasting and Postprandial Levels of Ghrelin, Peptide YY, Amylin, and Cholecystokinin (CCK) at Baseline, 10 Weeks, and 62 Weeks.



Obesity = a brain disease - Control Over Appetite Regulation



AGRP: agouti-related peptide; α-MSH: α-melanocyte-stimulating hormone; GHSR: growth hormone secretagogue receptor; INSR: insulin receptor; LepR: leptin receptor; MC4R: melanocortin-4 receptor; NPY: neuropeptide Y; POMC: proopiomelanocortin; PYY: peptide YY; Y1R; neuropeptide Y1 receptor; Y2R: neuropeptide Y2 receptor. Apovian CM, Aronne LJ, Bessesen D et al. *J Clin Endocrinol Metab.* 2015;100:342-362.

Managing Obesity as a Chronic Disease

5 FDA-approved medications on the market for chronic weight management

- Orlistat
- Lorcaserin
- Phentermine/Topiramate ER
- Naltrexone SR/Bupropion SR
- Liraglutide 3 mg

Orlistat

- Peripheral pancreatic-lipase inhibitor
- Common adverse events: gastrointestinal events, low fat-soluble vitamin levels



Phentermine

Mechanism of action and pharmacokinetics

- Phentermine is a sympathomimetic amine chemically related to amphetamine with significant anorectic activity and effects on the dopaminergic and noradrenergic nervous systems
- Appetite suppressant action of phentermine through the hypothalamus
- Phentermine absorption from the <u>resin complex formulation</u> is slower and peak blood concentration is decreased but prolonged, compared with the same dose of phentermine hydrochloride
- Phentermine is readily absorbed from the gastrointestinal tract and excreted substantially in urine
- The half-life of phentermine is about **25 hours**

CONQUER: Weight Loss Over Time

(Phentermine / Topiramate)



Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study^{1–3}

W Timothy Garvey, Donna H Ryan, Michelle Look, Kishore M Gadde, David B Allison, Craig A Peterson, Michael Schwiers, Wesley W Day, and Charles H Bowden



GARVEY ET AL

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Lorcaserin (Belviq[®])

- Approved 2012 (US FDA), post-marketing CV safety study
- Selective agonist at the 5HT_{2c} receptor
- BLOOM-DM 1-year RCT (Type 2 diabetics, metformin or SU)
 - Comparing: placebo vs. 10 mg lorcaserin daily vs. lorcaserin 10 mg twice daily
 - 5% (5 kg) lorcaserin bd group vs. 1.5% (1.6 kg) in placebo
 - HbA_{1c} reduction was **0.9** %
 - increased incidence of hypoglycemia on lorcaserin
- <u>adverse effects:</u> nausea, dizziness headache, serotonin syndrome, disturbance in attention
- potential concerns with regards to both carcinogenicity and valvulopathy



88

96 104

Naltrexone and Bupropion Rationally Designed Around MOA to Initiate and Sustain Weight Loss



COR-I, II: Body Weight, Change From Baseline

Placebo (N=511) NB16 (N=471) NB32 (N=471) Placebo (N=456) NB32 (N=702)



Completers: Placebo (N = 290): -1.8% , NB16 (N = 284): -6.7%* NB32 (N = 296): -8.1%* **Completers:** Placebo (N = 267): -1.4% NB32 (N = 434): -8.2%*

Drug Tolerability

Orlistatª	Lorcaserin ^b	Phentermine/ Topiramate ER°	Naltrexone SR/ Bupropion SR ^d	Liraglutide 3.0 mg ^e	
Steatorrhea symptoms	HeadacheDizzinessFatigue	 Paresthesias Dysgeusia Dizziness Dry mouth 	 Nausea Vomiting Headache Dizziness Insomnia 	 Nausea Vomiting Diarrhea Constipation Dyspepsia Abdominal pain 	
. Xenical PI 2013 ^[5] ; b. Belviq® PI 2012 ^[12] ;c. Qsymia® PI 2014 ^[9] ; d. CONTRAVE PI 2014 ^[10] ;					

e. Saxenda PI 2015.^[11]

Case 2 (short case)

<u>Hx:</u>

- 48 male
- Hx of bariatric surgery 10 years ago (Waikato, RYGP)
- Initial BMI 42kg/m2, post procedure 28kg/m2
- Generally well and active
- No DM2, all bloods normal
- Referred with syncopy (2x) after BF with sweets and coffee, diaphoresis, LOC, lasting 4min, not postictal
- Glucose recorded 2.8mmol/l at 2nd event

Questions:

- 1. What is the diagnosis?
- 2. What's the differential diagnosis?
- 3. How do we confirm it?
- 4. What can we do about it, and how do we treat him?
- 5. What is his prognosis and future risks?

Hypoglycemia After Bariatric Surgery

M27 Presented, April ■■■, 2018

 Identify staged management approaches for postbariatric hypoglycemia



Figure 1. Typical patterns of glycemic excursion in postbariatric hypoglycemia.



Figure: Potential mechanisms contributing to post-bariatric hypoglycaemia

The cornerstone of management of postbariatric hypoglycemia is medical nutrition therapy to reduce the stimulus for glycemic spikes and insulin secretion. Our team has recently published practical suggestions for medical nutrition therapy (11). In brief, because simple (high glycemic index) carbohydrates are rapidly digested and absorbed in a postbariatric patient, we advise complete avoidance of highglycemic-index carbohydrates. Instead, we recommend selecting controlled portions of low-glycemic-index carbohydrates

acarbose to slow absorption of glucose, reducing glycemic "spikes" and insulin secretion.

Somatostatin receptor ana- logues such as octreotide or pasireotide (12) can also reduce incretin and insulin secretion Diazoxide, which reduces insulin secretion, can also be helpful in doses of 50 to 100 mg three times per day but can be lin Some patients may benefit from surgical reversal of bariatric surgery,

partial pancreatectomy for severe postbariatric hypoglycemia (14,15), pancreatic surgery is no longer recommended due





SURGERY FOR OBESITY AND RELATED DISEASES

Surgery for Obesity and Related Diseases 13 (2017) 888-898

Review article

Medical nutrition therapy for post-bariatric hypoglycemia: practical insights

Emmy Suhl, M.S., R.D., C.D.E.^a, Sue-Ellen Anderson-Haynes, R.D.^a, Christopher Mulla, M.D.^{a,b,c}, Mary-Elizabeth Patti, M.D., F.A.C.P.^{a,b,c,*}

^aHypoglycemia Clinic, Joslin Diabetes Center, Boston MA
^bResearch Division, Joslin Diabetes Center, Boston, MA
^cHarvard Medical School, Boston, MA
Received November 1, 2016; accepted January 10, 2017

Weight Loss Surgery Improves T2DM

BMI

4





Bariatric Surgery vs Intensive Medical Therapy for T2DM: STAMPEDE Trial





Figure 1. Mean Percent Weight Change during a 15-Year Period in the Control Group and the Surgery Group, According to the Method of Bariatric Surgery.

I bars denote 95% confidence intervals.

Algorithm for the Treatment of T2DM as Endorsed by International Diabetes Organizations



Rubino F, et al. Diabetes Care. 2016;39:861-877.



Key Principles



Obesity Management is About Improving Health and Well-being, and not Simply Reducing Numbers on the Scale

- The success of obesity management should be measured in improvements in health and wellbeing rather than in the amount of weight lost.
- For many patients, even modest reductions in body weight can lead to significant improvements in health and well-being.

Key Principles



Success is different for every individual

- Patients vary considerably in their readiness and capacity for weight management.
- 'Success' can be defined as better quality-oflife, greater self-esteem, higher energy levels, improved overall health, prevention of further weight gain, modest (5%) weight loss, or maintenance of the patient's 'best' weight.

ASK for permission to discuss weight

Weight is a sensitive issue. Many patients are embarrassed or fear blame and stigma.

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- Be non-judgemental
- Explore readiness for change
- Use motivational interviewing
- Create weight-friendly practice



ASSESS obesity related risk and potential 'root causes' of weight gain

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- Advise on Obesity Risks
- Explain Benefits of Modest Weight Loss
- Explain Need for Long-Term Strategy
- Discuss Treatment Options



Advise on Treatment Options

• Average sustainable weight loss with behavioural intervention is about 3-5% of initial weight.





AGREE on realistic weight-loss expectations and on a SMART plan to achieve behavioural goals

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ASSIST in addressing drivers & barriers, offer education & resources, refer to provider, and arrange follow-up

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