The State of

Cardiometabolic

Disease & What are

the Targets to Mitigate

Risk?

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Disclosures

- Faculty: Sean Wharton
- Relationships with for-profit and not-for-profit interests:
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Disease Burden

To be able to discuss the disease burden of obesity, diabetes and cardiovascular disease

Conditions

Recognize the need to target weight, blood pressure, cholesterol, and smoking to reduce risk

Identify tools to mitigate cardiovascular risk

Treat Metabolic

Medical Complications of Increased Weight **Cognitive decline Pulmonary disease Mental health conditions** abnormal function obstructive sleep apnea hypoventilation syndrome Stroke **Acute Conditions** Cataracts COVID19

- disease diabetes dyslipidemia hypertension **Renal Failure**
 - Cancer
- Phlebitis/DVT (Blood Clots) venous stasis

Gout

Osteoarthritis

H1N1

Skin fungal/bacterial infections

Gynecologic abnormalities

polycystic ovarian syndrome

Nonalcoholic

steatohepatitis

infertility

steatosis

cirrhosis

Gall bladder disease

fatty liver disease

abnormal menses

urinary incontinence

Coronary heart

breast, uterus, cervix colon, esophagus, pancreas kidney, prostate



Obesity 650 million (13%) Globally 150 million (42%) U.S.A. 9 million (26%) Canada





9 million Canadians

Elisa Fabbrini t al. Hepatology 2010 Feb 51(2) 679-689. Wing RR. Evidence-based diabetes care. Hamilton: B.C. Decker Inc., 2000, pg. 252-76 Jehan et al. Sleep Med Disord. 2017; 1(4): 00019

Sleep Apnea 77%



Adipose Tissue Dysfunction

- Inability to store excess calories
- Cellular hypoxia
- Inflammation adipokines

Weight loss trajectories of 7,121 patients over 7.5 years Lifestyle Management (diet and exercise)



Patients who attended a physician-led multi-disciplinary clinical lifestyle weight management that predominantly focused on education and diet counseling management. WL, weight loss

Kuk J. Wharton S. Obes Sci Pract 2016:2:215–23

Weight stable (33.3%)

Minimal WL (36.9%) -2.3% WL

-21% WL

How much weight loss is needed to improve obesity-related complications?

3 to 10% Diabetes preventio 3 to >15% ripidaemia 3 to >15% Hyperglycaemia 5 to 10% GERD (females) 5 to 10% NAFLD 5 to 10% Osteoarthritis 5 to 10% Stress incontinence 5 to >15% Hypertension 5 to 15% PCOS 10 GERD (males) 10 Sleep apnoea 10 to 15% **Diabetes remission**

Weight loss required for therapeutic benefit (%)*

*Figure displays weight loss ranges examined in the studies (impact of >10% weight on NAFLD, and sleep apnea symptoms was not reported). BP, blood pressure; GERD, gastroesophageal reflux disease; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovary syndrome; TG, triglycerides.

Adapted from: AACE/ACE Obesity CPG, Endocr Pract. 2016;22(Suppl 3); Cefalu et al. Diabetes Care 2015;38:1567–82; Lean et al. Lancet 2018;391:541–51; Hannah & Harrison. Clin Liver Dis 2016;20:339–50.





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> 140 genetic regions are known to influence obesity traits

Genetics of Obesity

Neuropathology Associated with Obesity

Hypothalamic Hunger System

Mesolimbic Reward System



Dopamine Opioid Cannabinoid Receptors

Frontal Lobe Executive Function

- Ghrelin
- Leptin
- PYY
- GLP-1
- CCK
- Amylin



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Gut-Brain

Connection

GLP-1 and PYY delay gastric emptying and are potent anorexigenic gut hormones secreted by the L-cells in the small bowel in response to food ingestion

Leptin and insulin bind to their respective receptors in the arcuate nucleus to decrease food intake and increase energy expenditure

Gut microbiome – bacteria influences weight and messages to the brain

Metabolic

Adaptation

- Lower than expected metabolic rate
- Primarily after weight loss and then weight regain
- RMR stays low after regain of weight



Mitochondria

- **Dieting** depresses mitochondria function and gene expression
- **Bariatric surgery** improves the activity and function of mitochondria and gene expression.
- Differential Mitochondrial Gene Expression in Adipose Tissue Following Weight Loss Induced by Diet or Bariatric Surgery



Uncoupling Proteins for Obesity

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Chen et al. Mitochondrial uncoupler SHC517 reverses obesity in mice without affecting food intake. Metabolism. Volume 117, April 2021, 154724

Treating Obesity – Treats Type 2 Diabetes

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Eight-year weight losses with The look AHEAD study



Prevalence of Any Remission (Partial or Complete)

Weight loss across SCALE trials



Data are observed means; last observation carried forward at end of trial; N, number of individuals contributing to the analysis *Low calorie diet (total energy intake 1200–1400 kcal/day)

1. Pi-Sunyer et al. N Engl J Med 2015;373:11–22; 2. le Roux CW et al. Lancet. 2017;389:1399–1409; 3. Davies et al. JAMA 2015;314:687–99; 4. Blackman et al. Int J Obes (Lond) 2016;40:1310–19; 5. Wadden et al. Int J Obes (Lond) 2013;37:1443–51



Change in body weight (%) 0-56 weeks



FAS. Line graphs are observed means (±95% Wald CI). Statistical analysis is ANCOVA. Estimated means are calculated with missing observations at week 56 imputed using a regression method. CI, confidence interval; FAS, full analysis set

Davies et al. JAMA 2015:314:687-99







FAS LOCF. Change from baseline is observed mean change. Statistical analysis is analysis of covariance FAS, full analysis set; LOCF, last observation carried forward

Davies et al. JAMA 2015;314:687-99

Placebo

Naltrexone/Bupropion

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COR Phase 3 – Naltrexone/Bupropion

Weight Loss Results

a. BMI 30–45 kg/m2; b. BMI 27–45 kg/m2 with comorbidities. BMOD = behavior modification; ITT = intent-to-treat; DM = type 2 diabetes mellitus. CONTRAVE[®] (product monograph), February 12, 2018, Valeant Canada LP, Laval, QC. Greenway FL *et al. Lancet.* 2010;376:595-605. Wadden TA *et al. Obesity.* 2011;19:110-120. Hollander P *et al. Diabetes Care.* 2013;36:4022-4029. Apovian CM *et al. Obesity.* 2013;21:935-943.

Placebo

*p <0.001 vs. placebo.

Change in Glycemic Control Over 56 weeks

*P<0.001 vs placebo. HbA1c, hemoglobin A1C; NB32, naltrexone 32 mg/bupropion 360 mg Hollander P et al. Diabetes Care. 2013 Dec;36(12):4022-9.

Percentage of subjects reaching HbA1c target at week 56

target	Placebo (% subjects)	NB32 (% subjects)
7%	26.3%	44.1%*
.5%	10.2%	20.7%*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Once-Weekly Semaglutide in Adults with Overweight or Obesity

John P.H. Wilding, D.M., Rachel L. Batterham, M.B., B.S., Ph.D., Salvatore Calanna, Ph.D., Melanie Davies, M.D., Luc F. Van Gaal, M.D., Ph.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Barbara M. McGowan, M.D., Ph.D., Julio Rosenstock, M.D., Marie T.D. Tran, M.D., Ph.D., Thomas A. Wadden, Ph.D., Sean Wharton, M.D., Pharm.D., Koutaro Yokote, M.D., Ph.D., Niels Zeuthen, M.Sc., and Robert F. Kushner, M.D., for the STEP 1 Study Group*

Phase 3a Results – STEP Trials Effects of semaglutide 2.4 mg once-weekly in patients with obesity

*Statistically significant vs placebo. BW, body weight; IBT, intensive behavioural therapy.

STEP 2 – Diabetes - Semaglutide

Percentage change from baseline in body weight by week

Time since random allocations (weeks)

Time since random allocations (weeks)

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Observed mean percentage change from baseline in body weight over time for patients in the full analysis set during the in-trial observation period (from randomisation to last contact with trial site, regardless of treatment discontinuation or rescue intervention) and on-treatment observation period (during treatment with trial product [any dose of trial medication administered within the previous 2 weeks]). Data are for the full analysis set.

Error bars are ± standard error of the mean. Numbers below the panels are the number of patients contributing to the mean. Adapted from Figure 2. Comparison of bodyweight parameters for semaglutide 2.4 mg versus semaglutide 1.0 mg versus placebo, given once a week. Davies et al. Lancet 2021;epub ahead of print

aglutide veight by week

Confirmatory Secondary Endpoints Treatment policy estimand (2 of 3)

	Semaglutide 2.4 mg (N=404)	Semaglutide 1.0 mg (N=403)	Placebo (N=403)
HbA _{1c} , percentage points Week 68 mean ± SD Change from baseline to week 68 ± SE	6.4 (1.2): n=381 -1.6 ± 0.1	6.6 (1.1): n=376 −1.5 ± 0.1	7.8 (1.3); n=374 −0.4 ± 0.1
HbA _{1c} , mmol/mol Week 68 mean ± SD Change from baseline to week 68 ± SE	46.7 ± 12.9; n=381 −17.5 ± 0.7	48.4 ± 12.0; n=376 −15.9 ± 0.8	61.8 ± 14.4; n=374 −4.1 ± 0.8

Data are for the full analysis set for the treatment policy estimand (assesses treatment effect regardless of treatment discontinuation or rescue intervention). CI, confidence interval; ETD, estimated treatment difference; SD, standard deviation; SE, standard error. Adapted from Table 2. Co-primary, confirmatory secondary, and selected exploratory trial endpoints (treatment policy estimand). Davies et al. Lancet 2021;epub ahead of print

Treatment comparison [95% CI]; p value (for confirmatory analyses)

Semaglutide 2.4 mg – placebo ETD: -1.2 [-1.4 to -1.0]; p<0.0001

Semaglutide 2.4 mg – semaglutide 1.0 mg ETD: -0.2 [-0.3 to 0.0]

Semaglutide 1.0 mg – placebo ETD: -1.1 [-1.3 to -0.9]

Semaglutide 2.4 mg – placebo ETD: -13.5 [-15.5 to -11.4]; p<0.0001

Semaglutide 2.4 mg – semaglutide 1.0 mg ETD: -1.7 [-3.7 to 0.4]

Semaglutide 1.0 mg – placebo ETD: -11.8 [-14.0 to -9.7]

Treatment of Obesity based on Evidence and Biology

Medical Nutrition Therapy

Psychological (CBT) Pharmacotherapy Surgery

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Wharton S et al. Obesity in Adults CPG. CMAJ 2020 Aug 4;192:E875-91

Physical Activity

Current Treatments & Beyond

Current Medications

- Naltrexone/Bupropion
- GLP1 (Liraglutide) Once daily
- GLP1 (semaglutide) Once weekly
- Phentermine/Topiramate

Emerging Medications

- Amylin
- Combination Treatments GLP1/Amylin GLP1/GIP GLP1/Glucagon Agonist

Real World Study in Canada Liraglutide 3.0 mg n:311 patients

Wharton S et al. Obesity, June 2019. <u>https://doi.org/10.1002/oby.22462</u>

Effect of Naltrexone/Bupropion on weight in COR-I

Treatment with NB resulted in significant & sustained weight loss over 56 weeks

Completers: n=586

Figure on right republished with permission of the American Diabetes Association, from Hollander P et al,² © 2013; permission conveyed through Copyright Clearance Center, Inc. *P<0.001 vs placebo.

COR-I

BMOD=behavior modification; DM=diabetes mellitus; ITT=intent-to-treat; LS=least squares.

1. Contrave [prescribing information]. La Jolla, CA: Orexigen Therapeutics, Inc.; 2016. 2. Greenway FL et al. Lancet. 2010;376:595-605. 3. Wadden TA et al. Obesity. 2011;19:110-120. 4. Hollander P et al. Diabetes Care. 2013;36:4022-4029.

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Semaglutide 2.4mg Percentage change in body weight from baseline to week 58

*The treatment policy estimand assesses treatment effect regardless of treatment discontinuation or rescue intervention. Continuous end points were analyzed using analysis of covariance, with randomized treatment as a factor and baseline end point value as a covariate, and a multiple imputation approach for missing data.¹

[†]The trial product estimand assesses treatment effect if trial product was taken as intended (i.e. if all participants adhered to treatment and did not receive rescue intervention). End points were analyzed using a mixed model for repeated measurements. [‡]Not controlled for multiplicity.

1. Kushner RF, et al. Obesity 2020;6:1050-61. CI, confidence interval; ETD, estimated treatment difference.

Adapted from data presented in Table 2. Coprimary, Confirmatory, and Selected Supportive Secondary and Exploratory End Points for the Treatment Policy Estimand, and Table S2. Co-primary, Confirmatory and Selected Supportive Secondary Endpoints for the Trial Product Estimand.

Semaglutide 2.4mg Achievement of categorical body weight reduction at week 68

Bar graphs show the percentages of participants with an observation at the week 68 visit in whom body-weight reductions of at least 5%, 10%, 15%, and 20% were achieved from baseline to week 68 during the in-trial observation period and on-treatment observation period. Adapted from Figure 1C/D. Effect of Once-Weekly Semaglutide, as Compared with Placebo, on Body Weight.

How does semaglutide 2.4 mg affect other health parameters?

Results for the in-trial observation period and the treatment policy estimand. From STEP 1: Beneficial effects beyond weight loss vs. placebo, from baseline to week 68 CV, cardiovascular; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; IWQOL-Lite-CT: Impact of Weight on Quality of Life-Vt2; SF-36; Short Form 36.

Semaglutide 2.4 mg is Health Canada approved but is not commercially available.

1. Wilding et al. NEJM 2021; doi: 10.1056/NEJMoa2032183.

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Advise On obesity risks. Discuss the health benefits of obesity management.

Medical Nutrition Therapy (MNT)

MNT is used in managing chronic diseases and focuses on nutrition assessment, diagnostics, therapy and counselling. MNT should:

- a. be personalized and meet individual values, preferences and treatment goals to promote long term adherence
- b. be administered by a registered dietitian to improve weight-related and health outcomes

Physical Activity

30-60 mins of aerobic activity on most days of the week, at moderate to vigorous intensity, can result in:

- a. small amount of weight and fat loss
- b. improvements in cardiometabolic parameters
- c. weight maintenance after weight loss

(i) Remember nutrition and physical activity recommendations are important for all Canadians regardless of body size or composition.

The Three Pillars of Obesity Management that Support Nutrition and Activity

Treating the root causes of obesity is the foundation of obesity management refer to the 4M framework - mechanical, metabolic, mental and social milieu

Bariatric Surgery

 Procedure should be decided by surgeon in discussion with the patient.

- a. Sleeve gastrectomy
- b. Roux-en-Y gastric bypass
- Biliopancreatic diversion with/without duodenal switch

CRITERIA

BMI≥40 kg/m² or

BMI ≥35 - 40 kg/m² with an obesity (adiposity) related complication or

BMI ≥30 kg/m² with poorly controlled type 2 diabetes

Psychological & Behavioural Interventions in Obesity Management

MICHELE LALIBERTE, PH.D. ANDI E. M°CABE, PH.D. • VALERIE TAYLOR, MD, PH.E

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Vallis TM, Macklin D, Russell-Mayhew S. Canadian Adult Obesity Clinical Practice Guidelines: Effective Psychological and Behavioural Interventions in Obesity Management. Available from: https://obesitycanada.ca/guidelines/behavioural

Current & Emerging Pharmacotherapy Treatments

Pharmacotherapy should NOT be reserved for those who fail diet & exercise

Bariatric Surgery in Canada

CRITERIA

- BMI > 40
- BMI 35 40 with comorbidity

Guidelines recommend

• BMI > 30 in people with Type 2 Diabetes

Laurent Biertho MD et al. Bariatric Surgery: Surgical Options and Outcomes. Adult Obesity Guidelines https://obesitycanada.ca/guidelines/

Chronic Disease

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Conclusion The Science of Obesity

Clinical Practice

Obesity in prevalent, inflammation causes multiple complications, and it is understudied, likely due to bias

Science of obesity is complex and driven by brain neurochemistry

Diet and exercise alone and not sufficient for obesity treatment

Effective treatments for obesity are limited but increasing rapidly

Gut hormones and peptides are the primary targets for pharmacotherapy agents

Laurent Biertho MD et al. Bariatric Surgery: Surgical Options and Outcomes. Adult Obesity Guidelines https://obesitycanada.ca/guidelines/

Case Notes Session 1: Case 1

April 6, 2022

RECAP

 75 y/o female with uncontrolled diabetes, HLD, HTN and BMI 31 (82kg). A1C 9.3% on basal insulin and prandial insulin with largest meal. Possible lower health literacy and family concerns about hypoglycemia.

Medication	Dose	Frequency
Metformin	1000mg	BID
Insulin Glargine (Lantus)	24 units	QHS
Insulin Aspart (novolog)	2 units	with lunch
Atorvastatin	40mg	daily
Lisinopril	10mg	daily
Aspirin	81mg	daily

What information for every pt with diabetes do you need?

- 1.Weight
- 2. Kidney function
- 3. Age
- 4.Family hx of DM or autoimmune disease
- 5. Medications that increase insulin resistance
- 6. Lifestyle/Job/ diet/activity
- 7. Insurance
- 8. Other complications from diabetes

Individual Patient Characteristics

- BMI 31 (82kg)= so + insulin resistance
- GFR >60
- Age 75
- NO DKA
- Unknown Family hx
- High carb diet
- Medicare
- Concerns about insulin/hypoglycemia
- Possible microalbuminuria

First question:

Does this person produce insulin?

- Type 1 or Type 2?
- Insulinopenic or Insulin resistant ?

Type 2- most likely but as older think of possible relative insulinopenia

Second Question: • What is her A1c Goal?

• <8.0% (7.0 if possible without hypoglycemia)</p>

Individualizing Glycemic Targets

Figure 6.1—Depicted are patient and disease factors used to determine optimal A1C targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. A1C 7% = 53 mmol/mol. Adapted with permission from Inzucchi et al. (40).

Non-Pharm Intervention

- Screen for Depression
- Portion sizes for fruit
- Replace potatoes/ rice with smaller portion size and or beans or chick peas or lean protein
- Encourage activity after meal

Depression and Cognitive Impairment in Older Adults with Diabetes

Depression:

- PHQ-9
- GDS-15

Cognitive Impairment:

- Observed or reported changes
- Mini Mental Status Exam (MMSE)
- Mini-Cog
- Montreal Cognitive Assessment (MoCA)

Small apple=15 grams but larger 20-25 grams Banana=30 grams

Added Sugar vs Natural Sugar

- Quick and dirty > 10 grams of added sugar high and want as little as possible <5 or 0 grams
- Natural sugar limit to 10-15 gram per serving
- 3-5 serving a fruit

Serving Size ½ banana or apple

Lifestyle in older individuals with Obesity

- Assess sleep schedule since disrupted sleep could impact leptin and have down-steam impacts on insulin resistance
 - Goal 7-8 hours per night, avoid staying up too late
 - Rule out sleep apnea
- If any lower extremity issues that could impact walking consider sit and be fit exercises on Youtube or formal referral to physical therapy

- Exercise is critical for weight loss maintenance

 Use smaller plates, protein with each meal and each snack to help decrease hunger during weight loss and to also ensure preservation of muscle mass during weight loss. Eat protein first.

Advice to walk after meals is more effective for lowering postprandial glycaemia in type 2 diabetes mellitus

Measure	Post-meal walks	30 min walk	Difference (95% CI) (post-meal walks – 30 min walk) ^a	p value
All-meal iAUC ^b (mmol l ⁻¹ min ⁻¹)	453 ± 230	508 ± 270	0.88 (0.78, 0.99)	0.031
Breakfast iAUC (mmol l ⁻¹ min ⁻¹)	507 ± 298	540 ± 300	0.87 (0.72, 1.05)	0.153
Lunch iAUC (mmol l ⁻¹ min ⁻¹)	426 ± 259	444 ± 264	0.94 (0.80, 1.10)	0.416
Dinner iAUC (mmol l ⁻¹ min ⁻¹)	424 ± 240	537 ± 331	0.78 (0.67, 0.91)	0.001
FBG (mmol/l)	8.0 ± 2.61	7.9 ± 2.39	0.11 (-0.30, 0.52)	0.604
Mean BG (mmol/l)	9.3 ± 2.55	9.3 ± 2.46	0.01 (-0.29, 0.32)	0.932
MAGE (mmol/l)	4.7 ± 1.75	5.1 ± 2.08	-0.42 (-0.94, 0.10)	0.117
CONGA	8.4 ± 2.44	8.4 ± 2.32	-0.01 (-0.31, 0.29)	0.944
Glycaemic range (mmol/l)	12.7 ± 3.6	13.3 ± 4.07	-0.60 (-1.56, 0.36)	0.219

Reynoldset al . Diabetologia. 2016 Dec;59(12):2572-2578

CASE Question?

- Can this patient be managed with insulin sparing agents?
- Microalbuminuria vs need for Efficacy of 1.5-2% A1c lowering
- Yes consider SGLT2-I
- vs **GLP-1 RA**

- First assess how much insulin they are actually taking :
- -"If your blood sugars is in low 100's at bedtime what do you do with your insulin?"

Or

-"Many people are worried about low blood sugars do you ever take less insulin given a fear of low sugars?"

Pharmacologic intervention: Insulin and GLP-1-RA

- 0.3 u/kg basal- 0.3 x 82= 24 units
- ADA recommends do not increase over 0.5u/kg (41 units)
- A1c > 9.0
- Add Glp-1 Ra, stop prandial insulin
- Continue metformin consider convert 2 tablets 750mg XR daily in am with breakfast

Dual Therapy With SGLT-2I and GLP-1-RA ?

ACC/AHA CV Risk Calculator (2013)

Estimate 10-year risk for atherosclerotic cardiovascular disease

Questions

1.	Age?	75 Years
2.	Gender?	Female
3.	Race?	African-Amer
4.	Total Cholesterol?	113 mmol/L
5.	HDL Cholesterol?	39 mmol/L
6.	Systolic Blood Pressure?	110 mmHg
7.	Treatment for High Bloo	Yes
8.	Smoker?	No
9.	Diabetes?	Yes

Results Copy Results 10-Year Risk of Atherosclerotic Cardiovascular Disease (ASCVD)

100 %

10-Year Risk of ASCVD (%) for Someone of Same Age with Optimal Risk Factor Levels

11.2 %

Created by **Q**XMD

On Atorvastatin 40mg –high intensity On Lisinopril 10mg On ASA

ACC/AHA CV Risk Calculator (2013) (medscape.com)