

Reflections of the life journey of an obesity researcher

CABPS Canadian Obesity Weekend

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• Others:

- Obesity and diabetes advocate
- Editor-in-Chief Emeritus, Canadian Journal of Diabetes
- Founder, Obesity Canada
- > Past President, Canadian Association of Bariatric Physicians & Surgeons
- Employee of the University of Calgary
- I aim to use person-first and inclusive language in this presentation. Please contact me if you notice anything that could be improved: <u>dcwlau@ucalgary.ca</u>

CanMEDS Roles Covered: David C.W. Lau "Canadian Obesity Weekend 2022"

Х	Medical Expert (as <i>Medical Experts</i> , physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. <i>Medical Expert</i> is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
Х	Communicator (as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
Х	Collaborator (as <i>Collaborators</i> , physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
Х	Leader (as <i>Leaders</i> , physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
Х	Health Advocate (as <i>Health Advocates</i> , physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
Х	Scholar (as <i>Scholars</i> , physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
Х	Professional (as <i>Professionals,</i> physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)



Obesity is an age-old problem

- From the Old Testament written about 721 B.C.
 - Judges 3:17 "and he presented the tribute to Eglon, King of Moab. Now Eglon was a very fat man"
- Hippocrates from the 4th-5th century B.C. wrote:
 - > "All disease begins in the gut
 - Everything in excess is opposed by nature. If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health
 - > Let food be thy medicine and medicine be thy food
 - It is very injurious to health to take in more food than the constitution will bear when, at the same time one uses no exercise to carry off this excess





Venus of Lespugue

- A 25,000 year-old prehistoric nude female figurine carved from tusk ivory
- Discovered in 1922 in the Rideaux cave of Lespugue in the French Pyrenees
- It is 6 inches (150 mm) tall and currently on display at the Musée de l'Homme in Paris



Pathogenesis of obesity



1 ton of food = **1** million calories in **1** year



Genetics and Environment

CNS control (homeostatic, hedonic, cognitive) Afferent neurohormonal signals from gut, pancreas, adipose tissue and muscle Resting energy expenditure Physical activity Diet-induced thermogenesis Caloric losses (GI tract & kidneys)

Adipocytes: Energy storage depot





Adipose tissue development and growth



- White adipose tissue (WAT) is derived from the mesoderm and first appears in the second trimester of pregnancy
- Interscapular brown adipose tissue (BAT) is found in the first few years of life but decreases with age, and may be different from beige thermogenic adipocytes
- In lean adults, the entire WAT depot ranges from 20 to 30 kg in women (30 to 40% of total body mass) and 10 to 20 kg in men (15 to 25% of total body mass)
- Adipose tissue mass can increase dramatically in obesity, from 40 to > 100 kg

Adipose tissue depots



- Subcutaneous fat accounts for about 85% of total body fat
- Intra-abdominal or visceral fat (15%)
- Visceral adipose tissue is the "ugly fat" associated with decreased insulin sensitivity, increased lipolytic activity, lower angiogenic potential, increased expression of proinflammatory adipokines, and decreased production of the "good" hormones





Visceral

Five-decade history of adipose cell biology

- Early 1970s:
 - > Fat is a passive repository for energy storage
- Mid-1970s
 - Discovery and identification of preadipocytes in 1976
 New insights into adipose cell biology and growth cycle
- 1980s: Endocrine and paracrine regulation of fat cell growth
 > Regional differences in cell proliferation and differentiation
 > Fat is an active paracrine and juxtacrine organ





Five-decade history of adipose cell biology

- 1990s: Transcriptional control of adipogenesis
 - > Discovery of leptin and endocrine control of appetite
 - Molecular insights into the control of adipose cell development and growth
- 2000s:
 - ➢ Fat is an endocrine organ
 - >Adipose tissue dysfunction and cardiometabolic risk
 - Genetics of obesity
 - Appetite regulation
 - Bariatric surgery for type 2 diabetes
 - Pharmacotherapy for obesity



Adipogenesis



- Involves the recruitment, proliferation and differentiation of preadipocytes to acquire the phenotype of mature adipocytes
- Associated with the production of a large number of proteins that function as signalling molecules in glucose and lipid metabolism, and energy homeostasis





Hypertrophic

Hyperplastic

Paracrine regulation of adipose tissue growth



- Paracrine interaction among preadipocytes, mature adipocytes and microvascular endothelial cells may play a role in the regulation of adipose tissue development and growth
- Regional fat depot development and growth are under paracrine, endocrine and dietary influences

Lau DCW et al. J Clin Invest 1987;79:632-636; Shillabeer G et al. J Clin Invest 1989;84:381-387 Shillabeer G et al. Am J Physiol 1990;258:E368-E376; Eslami Varzaneh F et al. Metabolism 1994;43:906-912 Shillabeer G, Lau DCW. J Lipid Res 1994;35:592-600; Li ZH et al. Cell Biol Int 1998;22:253-270



Adipose tissue

Obesity increases adipocytokine production in adipose tissue and cardiometabolic risk

ST.

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Lau DCW et al. Am J Physiol 2005;288:2031-2041; Eckel RH et al. Lancet 2005;365:1415-28

Adipocyte is an endocrine organ





Kahn BB, Flier J JCI 2000;106:473-481

Congenital Leptin Deficiency





Farooqi IS, et al. New Engl J Med 1999;374:879-884





Fat cell size and cardiometabolic complications





Adipocyte hypertrophy

- Impairs adipocyte differentiation potential and adipogenesis rate, adipose tissue inflammation and altered adipokine secretion
- Is associated with dysregulation in glucose, lipid metabolism, ectopic fat and cardiometabolic complications

Ye RZ et al. Endocrine Rev 2021;bnab018, https://doi.org/10.1210/endrev/bnab018

Adipose tissue composition

- A dynamic organ that can respond to alterations in energy stores through adipocyte hypertrophy and hyperplasia
- Composed of
 - Large mature adipocytes (50%)
 - Preadipocytes
 - Endothelial cells
 - Macrophages and inflammatory cells (~5-10%)
 - Extracellular matrix



Adapted from Ouchi N, et al. Nature Rev Immunol 2011;11:85-97

Brown and beige fat



- Brown adipose tissue (BAT) exists in small quantities in adults, and is involved in whole-body energy homeostasis through non-shivering thermogenesis
- BAT is metabolically activated by cold exposure but its activity is significantly lower in overweight or obese subjects than in lean subjects
- Beige adipocytes are thermogenic adipocytes in white adipose tissue that can be induced by chronic exposure to cold temperatures and, to some extent, exercise
- Further elucidation of the potential roles of brown/beige fat in the regulation of whole-body energy metabolism and glucose and lipid homeostasis could potentially open new avenues of obesity management

Mechansims linking obesity to cardiometabolic diseases

Mechanisms linking obesity to cardiometabolic diseases

- ↓ Fitness
- Chronic positive energy balance
- Genetic factors



 ↑Adipocyte size



Ectopic fat
 ↑(e.g. liver)
 ↓Leg fat

Adipose tissue

inflammation

There is a large variation in the individual risk to developing obesity-related comorbid diseases

10-20% of people with obesity are "metabolically healthy"

Blüher M. Endocr Rev 2020;41:1-16 https://doi.org/10.1210/endrev/bnaa004



Adverse signals:

Adipokines

• Type 2 diabetes

Hypertension

• Dyslipidemia

NAFLD

• CVD

- Metabolites
- Immune cells

Phenotypic traits associated with metabolically healthy versus unhealthy obesity



Insulin resistance Higher markers of inflammation Adipose tissue dysfunction



Blüher M. Endocr Rev 2020;41:1-16 https://doi.org/10.1210/endrev/bnaa004

Normal inflammatory markers

Normal adipose tissue function

Pathways through which excess adiposity leads to major risk factors and common chronic diseases





Heymsfield SB, Wadden TA. N Engl J Med 2017;376:254-266

Monogenic mutations in hypothalamic obesity





- 1. Barsh GS, Schwartz MW. Nat Rev Genet. 2002;3:589-600
- 2. Farooqi IS et al. J Clin Invest. 2002;110:1093-1103
- 3. Krude H et al. Nat Genet. 1998;19:155-157
- 4. Farooqi IS et al. N Engl J Med. 2003;348:1085-1095

Rising global prevalence of obesity



- Worldwide obesity has nearly tripled since 1975
- In 2016, more than 39% or 1.9 billion adults, 18 years and older, had overweight
- Over 13% or 650 million people had obesity
- Over 340 million children and adolescents aged 5-19 had overweight or obesity in 2016
- 38 million children under the age of 5 had overweight or obesity in 2019

Prevalence of obesity in Canada



- The prevalence of obesity has increased 3-fold since 1985
- Overweight affected 34% of adults or 10.6 million adults in Canada in 2016
- Obesity affected 26.4% or 8.3 million adults
- Since 1985 severe class 3 obesity (BMI ≥ 35 kg/m²) increased 455% and affected an estimated 1.9 million Canadian adults
- One in three children and/or youths between 6 and 17 years have overweight or obesity, an increase from one in four in 1978/79

Wharton S, Lau DCW, Vallis M, et al. CMAJ 2020;192:E875-E891 <u>https://doi.org/10.1503/cmaj.191707</u> Twells LK, Janssen I, Kuk JL. Canadian Adult Obesity Clinical Practice Guidelines: Epidemiology of Adult Obesity. Available from: <u>https://obesitycanada.ca/guidelines/epidemiology</u>. Accessed April 4, 2021

Management of obesity is more effective with an interdisciplinary care team





Fitzpatrick SL et al. Am J Med. 2015; pii: S0002-9343(15)00691-9

Advances in obesity treatment



- An interdisciplinary weight management clinic was established at the Calgary Foothills Hospital in 1986, the first in the country
- Canada was one of the first countries to adopt BMI and waist circumference measurements to classify and treat obesity in 2003
- Obesity Canada was founded in 1999 as a not-for-profit organization to promote obesity research, treatment, public awareness and advocacy
- Obesity Canada published the world's first evidence-based CPGs on obesity management and prevention in 2007
- Bariatric surgery for type 2 diabetes was introduced in the 2000s
- Effective and safe weight management medications have become available over the past decade

Rationale for guidelines update

CMAJ·JAMC

April 10, 2007, Vol. 176, No. 8 • Le 10 Avril 2007, Vol. 176, N° 8

2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [summary]

www.cmaj.ca/cgi/content/full/176/8/S1/DC1

Lau DCW et al. Can Med Assoc J 2007;176 (8 suppl):S1-S13

Since the 2006 evidence-based CPGs there have been advances in

- Epidemiology
- Determinants
- Pathophysiology
- Assessment
- Prevention and treatment of obesity
- Shift in the focus of obesity management toward improving patient-centred health outcomes, rather than weight loss alone



Life expectancy and healthy life-years decrease with increasing BMI



Compared to a woman aged 20–39 with a normal BMI:

The predicted lifespan is:

5.6 years less with class I obesity 6.1 years less with class II-III obesity



Compared to a man aged 20–39 with a normal BMI:

> 5.9 years less with class I obesity 8.4 years less with class II-III obesity

The number of healthy years is: 14.6 years less with class I obesity 19.1 years less with class II-III obesity The number of healthy years is: 11.8 years less with class I obesity 18.8 years less with class II-III obesity

Normal BMI: <25 kg/m²; Class I Obesity: BMI of 30 to 35 kg/m²; Class II-III Obesity: BMI of ≥35 kg/m²



Grover S et al. Lancet Diabetes Endocrinol. 2015;3:114-122

OBESITY IN ADULTS

A clinical practice guideline

BMI IS NOT AN ACCURATE

TOOL FOR IDENTIFYING

OBESITY-RELATED COMPLICATIONS

Obesity complex disease in which abnormal or excess body fat impairs health Effects: V health ▼ quality of life ▼ lifespan People with obesity increased complications and mortality independent experience weight bias and stigma of weight or BMI Weight bias thinking that people with Stigma acting

heliefs

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THE PATIENT JOURNEY IN OBESITY MANAGEMENT ASK ADVISE ON PERMISSION MANAGEMENT ... "Would it be all right Medical nutrition therapy if we discussed vour weight?" Asking permission and evidence-based nutrition therapy · Shows compassion and empathy Exercise Builds patient-provider trust most davs **ASSESS** THEIR STORY Psychological Goals that matter to the patient Cognitive approach For weight loss Obesity classification to behaviour change and to help (BMI and waist circumference) maintain weight Manage sleep Disease severity time and stress (Edmonton Obesity Staging System) · Psychotherapy if appropriate Treating the root causes of weight gain is the foundation of obesity management



Evidence-informed CPGs led jointly by Obesity Canada and Canadian Association of Physicians and Surgeons

- Guideline development 2017-2020
- 60 authors
- People living with obesity
- 80 recommendations
- 24 chapters
- Living document update

Wharton S, Lau DCW, Vallis M et al. CMAJ 2020;192:E875-E891 https://doi.org/10.1503/cmaj.191707

Focus on patient-centred

health outcomes versus weight loss alone

cmal.ca

The 25 Most Read Articles from 2020

GUIDELINE

Obesity in adults: a clinical practice guideline*

RESEARCH

2

3

Impact of climate and public health interventions on the COVID-19 pandemic: A prospective cohort study

RESEARCH

Effect of moist heat reprocessing of N95 respirators on SARS-CoV-2 inactivation and respirator function

ANALYSIS

Smartphones, social media use and youth mental health*

REVIEW

Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of SARS-CoV-2 infection*

Obesity in adults: Clinical practice guidelines

2007...

"Obesity is defined by a BMI of ≥30 kg/m²"



Now...

"Obesity is a complex chronic disease in which abnormal or excess body fat (adiposity) impairs health, increases the risk of long-term medical complications and reduces lifespan."



Focus on **patient-centric care**: determining the root causes of obesity should involve a patient's **overall health and experience**, and move away from "eat less, move more"

Lau DCW, Douketis J, Morrison KM, et al. CMAJ 2007;176(8 suppl):S1-13 Wharton S, Lau DCW, Vallis M, et al. CMAJ 2020;192:E875-E891 <u>https://doi.org/10.1503/cmaj.191707</u>



2020 CPGs update: Key messages

- Obesity is a prevalent, complex, progressive and relapsing chronic disease, characterized by abnormal or excessive body fat (adiposity), that impairs health
- People living with obesity face substantial bias and stigma, which contribute to increased morbidity and mortality independent of weight or body mass index (BMI)
- Obesity care should be based on evidence-based principles of chronic disease management, must validate patients' lived experiences, move beyond simplistic approaches of "eat less, move more," and address the root drivers of obesity
- People living with obesity should have access to evidence-informed interventions, including medical nutrition therapy, physical activity, psychological interventions, pharmacotherapy and surgery



Canadian CPG: Obesity management options

Medical Nutrition Therapy (Diet)

Physical Activity



Psychological and behavioural interventions

- Behaviour modification, cognitive reframing, and values-based strategies
- Manage sleep, time, and stress
- Psychotherapy if applicable

Pharmacotherapy

- BMI ≥ 30 kg/m²
 OR
- BMI ≥ 27 kg/m² with adiposity-related complications

BMI ≥ 40 kg/m²

OR

 BMI ≥ 35 kg/m² with at least 1 adiposityrelated complication

Bariatric surgery

Wharton S, Lau DCW, Vallis M et al. CMAJ 2020;192:E875-E891 <u>https://doi.org/10.1503/cmaj.191707</u>

Stepwise approach to obesity treatment

BMI 25–26.9 kg/m ² BMI 27–29	9.9 kg/m ² BMI 30–34.9 kg/m ²	BMI 35–39.9 kg/m ²	BMI ≥40 kg/m²
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BMI, body mass index

Yumuk V et al. Obes Facts 2015;8:402–24 * Wharton S, Lau DCW, Vallis M et al. CMAJ 2020;192:E875-E891 <u>https://doi.org/10.1503/cmaj.191707</u>



Long-term weight loss is modest and challenging



Hormonal and metabolic adaptation following weight loss



Sumithran P et al. N Engl J Med. 2011;365:1597-1604 CALGARY Schwartz A, Doucet E. Obes Rev. 2010;11:531–547

Nordmo M et al. Obes Rev 2020;21:e12949

Small changes in lifestyle approach are ineffective for weight loss

- 320 sedentary adults with overweight or obesity were randomized to a small change in lifestyle approach (SCA, n = 160) by increasing daily step count of 2000 steps with a decrease in energy intake of 100 kcal/day with group and individual support, or monitoring alone (MA, n = 160) for 2 years, followed by a passive 1-year follow-up
- Primary end-point was change in weight from baseline at year 2 and year 3
- Waist circumference and cardiorespiratory fitness were also measured

Results:

- Body weight change between SCA and MA was significant at 3, 6, 12 and 15 months, but not at year 2 and year 3 for both men and women
- Changes in waist circumference and cardiorespiratory fitness were not significantly different







Ross R et al. CMAJ 2022;194:E324-E331

В

С

Unmet needs in management of obesity

Obesity treatment options Bariatric surgery Medium High Mean weight loss Pharmacotherapy (treatment gap) Low

Diet and exercise

Medium

Complexity of treatment

Low

High

~6.5 million (24%) of Canadian adults have obesity (BMI >30)

Less than 1% of those people receive a prescription for an anti-obesity medication

~6,000 bariatric surgeries on average every year (up 300%) over the last 5 years)

Sources: Population & Obesity counts - Statistics Canada 2013 Zhang S et al. Obes Sci Pract. 2016;2(2):104–114 Bariatric Surgery count from CIHI Bariatric Surgery in Canada 2014



Stepwise approach to obesity treatment





BMI, body mass index

Yumuk V et al. Obes Facts 2015;8:402–24

* Wharton S, Lau DCW, Vallis M et al. CMAJ 2020;192:E875-E891 <u>https://doi.org/10.1503/cmaj.191707</u>



Pharmacotherapy targets of anti-obesity medications



5-HT2c, 5-hydroxytryptamine; D/NE, dopamine/norepinephrine; GABA-R, gamma-aminobutyric acid receptor; GLP-1R, glucagon-like peptide-1 receptor; MOP-R, Mu-Opioid receptor



Patel D. Metabolism 2015;64:1376-85

Satiety and Clinical Adiposity – Liraglutide Evidence (SCALE) Phase 3a program: Key efficacy outcomes





*Following lifestyle intervention induced weight loss of ≥5% over a 12 week run in period

1. Pi-Sunyer X et al. *N Engl J Med* 2015;373:11-22; 2. le Roux CW et al. *Lancet* 2017;389:1399-1409; 3. Davies MJ et al. *JAMA* 2015;314:687-99; 4. Wadden TA et al. *Int J Obes (Lond)* 2013;37:1443-1451; 5. Blackman A et al. *Int J Obes (Lond)* 2016;40:1310-1319

Summary: Weight loss across STEP 1-5 and 8 trials

Effects of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity



Placebo

Greater weight loss leads to improved health outcomes



Towards greater weight loss and overall health improvement



CV, cardiovascular; GERD, gastro-oesophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OA: osteoarthritis; OSA, obstructive sleep apnea syndrome; PCOS, polycystic ovary syndrome; TG, triglycerides

Garvey WT et al. Endocr Pract 2016;22(Suppl. 3):1–203; Look AHEAD Research Group. Lancet Diabetes Endocrinol 2016;4:913–21; Lean ME et al. Lancet 2018;391:541–51; Benraoune F and Litwin SE. Curr Opin Cardiol 2011;26:555–61; Sundström J et al. Circulation 2017;135:1577–85

Cagrilintide and change in body weight (%)

Baseline to week 26 – Primary estimand*



*Primary estimand assumes that all participants were adherent to treatment. Mean (SEM) change from baseline in body weight (%) by treatment week – MAR-MI – treatment adherent – full analysis set. ANCOVA estimates using the primary analysis. ANCOVA, analysis of covariance; MAR-MI, missing at random multiple imputation; SEM, standard error of the mean



Lau DCW et al. Lancet 2021; https://doi.org/10.1016/S0140-6736(21)01751-7

Cagrilintide-Semaglutide: Estimated mean change in percentage body weight from baseline to week 20



*P value <0.01 vs pooled or matched placebo



Enebo LB, et al. Lancet 3032;397:1736-1748

Major target tissues/organs for current and future weight loss pharmacotherapeutic approaches





Angelidi AM et al. Endocr Rev, bnab034 https://doi.org/10.1210/endrev/bnab034

Potential noninvasive weight loss strategies



Central nervous system

CNS Secreted neuropeptides and antagonists

Tesofensine

- Oxytocin
- NPY antagonists
- Methylphenidate
- GDF-15

Endocannabinoid system agents

 CB1R Antagonists (rimonabant, AM251, AM6545, JD5037) Agents targeting GPR

(GPR55, GPR18, GPR119)



Adipose tissue

- Leptin
- B3-adrenoreceptor agonists (mirabegron)
- PPAR-γ agonists
- Other adipokines

GI system

Gut-derived hormones and gut-brain axis

• CKK

- PYY analogues
- OXM
- Glicentin
- Ghrelin
- Secretin
- · GLP-1 agonists (exenatide, liraglutide, lixisenatide, dulaglutide, albiglutide, semaglutide)

Combinations

- Dual agonists (GLP-1/glucagon, GLP-1/GIP)
- Triple agonists (GLP-1/GIP/glucagon, GLP-1/OXM/PYY)
- Synthetic GLP-1/glucagon coagonists (Cotadutide, SAR425899)
- Synthetic GLP-1/GIP coagonists (tirzepatide)
- DACRAs

Other gut peptide-related approaches

- FGF21 analogues · Bile acids

Pancreas

- Insulin
- Amylin analogues



Angelidi AM et al. Endocr Rev, bnab034 https://doi.org/10.1210/endrev/bnab034

- CRISPR systems TALENs

antiobesity vaccines

Stepwise approach to obesity treatment



BMI, body mass index

Yumuk V et al. Obes Facts 2015;8:402–24

* Wharton S, Lau DCW, Vallis M et al. CMAJ 2020;192:E875-E891 <u>https://doi.org/10.1503/cmaj.191707</u>









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Bariatric surgery: Surgical options



Adjustable gastric band (restrictive)

An inflatable band is used to create a small pouch, which limits food consumption



Sleeve gastrectomy (restrictive)

Permanently removes most of the stomach, leaving a sleeve-shaped pouch; results in \downarrow ghrelin (hunger hormone)

Newer procedures:

- Single anastomosis
- Duodenal switch
- Gastric plication
- Single-anastomosis gastric bypass
- Endoscopic therapies
 Intra-gastric ballons
 - Endoscopic bypass
 - Endoscopic sleeve gastrectomy
 - Aspiration therapy



Roux-en-Y gastric bypass (restrictive & malabsorptive)

Creates a smaller stomach and bypasses part of the intestine; results in \uparrow GLP-1 (satiety hormone)



Bileopancreatic diversion (restrictive & malabsorptive)

Similar to Roux-en-Y gastric bypass. A variant called a duodenal switch retains the pyloric valve



Adapted from the Canadian Adult Obesity Clinical Practice Guidelines [Bariatric surgery: surgical options and outcomes. Biertho L, et al. 1-13, copyright notice] with permission from Obesity Canada/ Obésité Canada

Swedish Obese Subjects trial: 20-year weight loss





SOS trial

- Prospective, matched surgical intervention study (n=4047) recruited from 1987 to 2001
- Age 37-60 years
- BMI ≥ 34 kg/m² for men and ≥38 kg/m² for women
- Banding, vertical banded gastroplasty (VBG) or gastric bypass (GBP) surgery
- 12-25 year follow-up duration

Benefits of bariatric surgery



Photo Source: American Society for Metabolic & Bariatric Surgery



SOS trial: Mortality and diabetes remission









(b)

SOS. Incidence of diabetes over 2 and 10 years



Sjöström L. J Int Med 2012;273:219-234 DOI:10.1111/joim.12012



Time (years)

Bariatric surgery and diabetes remission



- Open label, single centre RCT
- 10-year follow-up of 60 patients randomized to bariatric surgery (20 RYGB, 20 BPD) or medical therapy (20)
- 10-yr diabetes remission rates
 - ➢ 50% for BPD
 - ➢ 25% for RYGB
 - 5.5% for medical therapy
- Both surgical groups had better quality of life total and subdomain scores (assessed by SF-36)
- Both surgical groups had fewer diabetesrelated complications than medical therapy (RR 14.4)
- BPD group had more serious adverse events (OR 2.7)

Mingrone G et al. Lancet 2021;397:293-304

Physical

100

Emotional role

RR=14.4 (95% CI 3.6-57.5)

functioning

Physical

Bodily

pain

Vitality

Microvascular complications Macrovascular complications

Surgical procedures

Total score

General health

100

75

50

25-

61%

11%

Medical therapy

STAMPEDE: Changes in diabetes control from baseline to 5 year



8.8 (8.9) 7.5 (6.9) 7.7 (7.4) 8.2 (7.9)

8.9 (8.5) 7.2 (6.5) 7.3 (6.8) 8.5 (7.1) 8.5 (8.2) 8.3 (8.0)

9.5 (9.1) 6.6 (6.7) 6.8 (6.8) 7.1 (6.7) 7.2 (6.8) 7.3 (7.1)

9.4 (9.2) 6.5 (6.2) 6.6 (6.4) 6.8 (6.6) 6.8 (6.5) 7.3 (7.1)

8.8 (8.6) 8.8 (8.0)

Glycated Hemoglobin Level (%)

tomy

Change in BMI from Baseline

Mean Value

Gastric bypass

Sleeve gastrec-

34.1

26.9

26.9

37.0

36.0

35.0

27.4

27.7

348

28.2

28.1

28.9

29.3

Medical ≥35

Surgical <35

Surgical ≥35

28.6

28.2

at Visit

tomy

STAMPEDE randomized clinical trial

 150 patients with T2D and BMI 27-43 kg/m² randomized to surgery (Roux-en-Y bypass or sleeve gastrectomy) or intensive medical therapy

13

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- Mean age 49±8 years, 66% women
- BMI 37±3.5, HbA1c 9.2±1.5%
- 134/149 completed 5-year follow-up
- Diabetes remission (HbA1c <6% & no meds)
 - \blacktriangleright Gastric bypass 29% (n=14/49)
 - Sleeve gastrectomy 23% (n=11/47)
 - \succ 5% (n=2/38) medical therapy

Schauer PR et al. N Engl J Med 2017;376:641-651

Physiological mechanisms underlying weight loss following vertical sleeve gastrectomy and Roux-en-Y gastric bypass



Akalestou E et al. Endocr Rev, 2022;43(1):19–34 https://doi.org/10.1210/endrev/bnab022

Physiological mechanisms underlying weight loss following Roux-en-Y gastric bypass and sleeve gastrectomy





Calorie restriction	+
Vagal nerve signaling	1
Taste and smell changes	+
Food aversions	+
Ghrelin	\mathbf{A}
Bile acid secretion	↑
Intestinal glucose uptake	
Fat malabsorption	
GLP-1	1
PYY3-36	1
GIP	
Oxyntomodulin	
FGF-19	1
ССК	Ť
Gastrin	↑
Neurotensin	
	Calorie restriction Vagal nerve signaling Taste and smell changes Food aversions Ghrelin Bile acid secretion Intestinal glucose uptake Fat malabsorption GLP-1 Fat malabsorption GLP-1 Oxyntomodulin FGF-19 CCK Gastrin Neurotensin



Pucci A, Batterham RL J Endo Invest 2019;2:117–128

RYGB: Timeline of mechanisms in weight loss and diabetes resolution



Holst JJ et al. SOARD 2018;14(5):708-714



Bariatric surgery: Summary and future directions

- Bariatric surgery remains an important treatment option for obesity
- Proper patient selection and preparation are critical for successful surgical outcomes
- Bariatric surgery is associated with weight-dependent and weightindependent benefits
- Bariatric management should be offered to all post-surgical patients
- Understanding the mechanisms of weight loss and metabolic benefits following surgery will enable better patient selection
- Identify who are the responders to surgery
- Explore role of endoscopic therapies
- More RCTs and longer-term studies are needed



Summary and key messages

- Obesity is a chronic relapsing chronic disease characterized by abnormal or excessive body fat that impairs health
- Advances in adipose cell biology and obesity research continue to inform state-ofthe-art management of obesity and type 2 diabetes
- Bariatric medicine embraces the convergence of bariatric physicians and surgeons
- Best care for people living with overweight and obesity will continue to improve with new knowledge and knowledge translation
- Access and public coverage of obesity treatment remain a challenge
- A career as a clinician-investigator in academia is challenging but rewarding, and highly recommended
- Future of CABPS is bright and promising in improving and advancing the health of people living with obesity



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