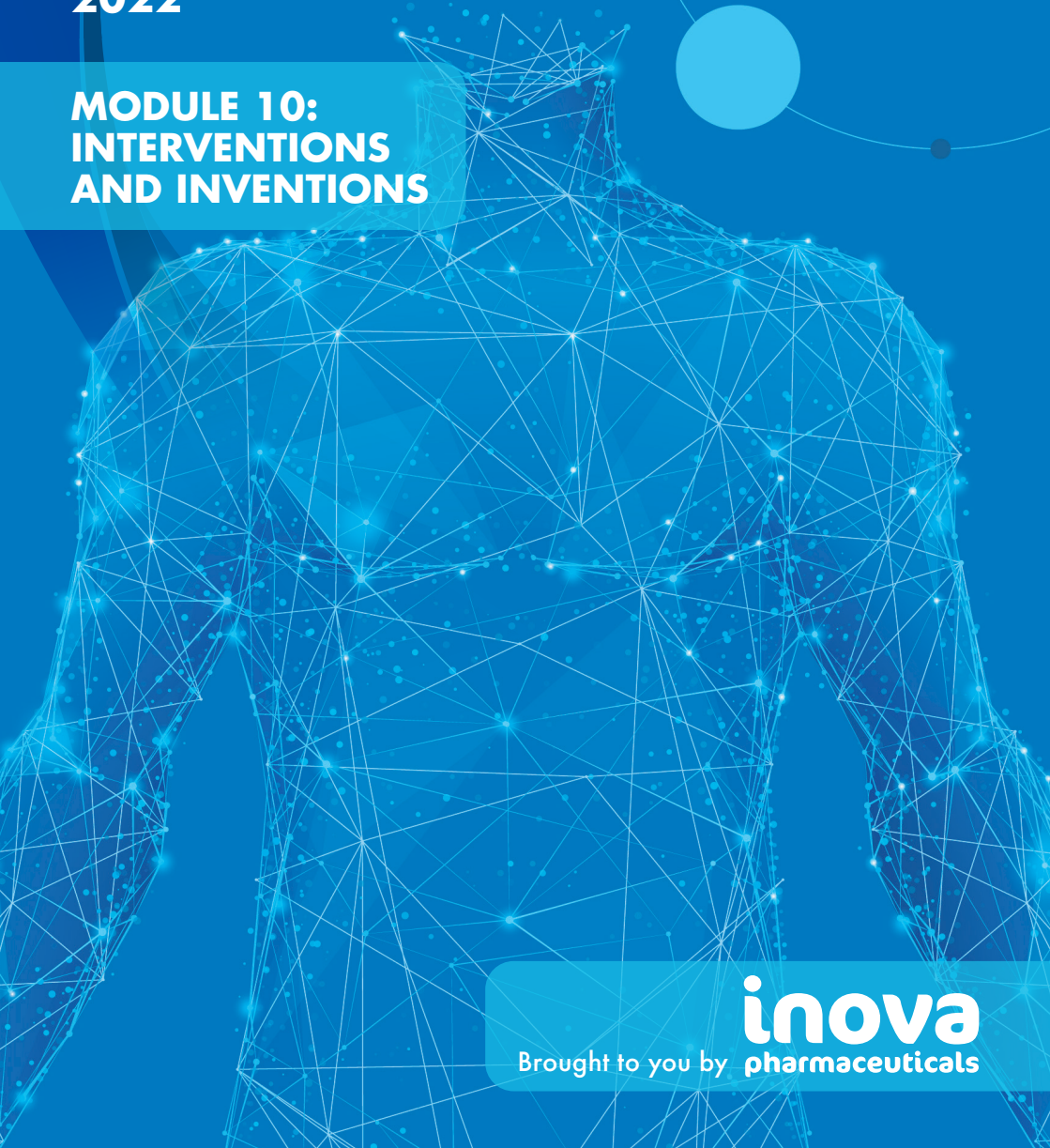


OBESITY, METABOLIC SYNDROME & BEYOND

2022

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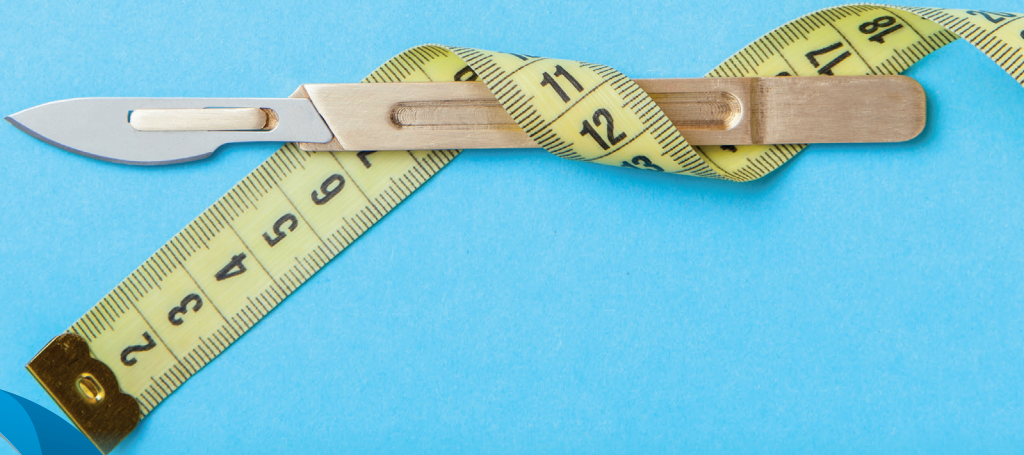
MODULE 10: INTERVENTIONS AND INVENTIONS



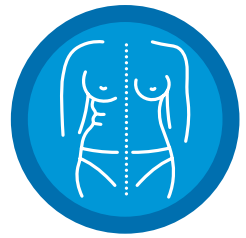
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SURGICAL PROCEDURES AND FUTURE DEVELOPMENTS IN OBESITY THERAPY



INTRODUCTION

Whenever we embark on obesity therapies there are 3 fundamental rules to consider:

1. Firstly, treat the **presenting co-morbidity** e.g. hypertension
2. Secondly, treat the **underlying cause** e.g. MC4r with Setmelanotide
3. Thirdly, **lifestyle** is your number 1 medicine – a healthy, plant-based diet (1500 Calorie/day with 5:2 fasting and low in soya); 30 minutes a day of physical activity (simply walking); daily stress reduction; and 7 hours of sleep each night.

Now we have reached an interesting point in the management of obesity. Most (>90 %) of the epigenetics and the medical therapies for obesity are based on manipulating the **BRAIN** specifically the periventricular hypothalamus. 40 % of therapies are aimed at reducing **insulin resistance**. When it comes to surgical interventions we go back to **THE GUT**. Yes, there are some weird way-out concepts where some nutty scientist has suggested brain implants to reduce ghrelin activity and thereby stop hunger.

The idea behind surgery stems from the early **Billroth gastrectomies** of the 70-80's. These were gastric operations for peptic ulcer disease as it predated the use of proton pump inhibitors (PPI's) and the eradication of *Helicobacter pylori* infections. We now treat the pH and the Hp!

The patients who underwent these **invasive operations** all lost weight and also managed to keep the weight off. As they aged there was a very slow development of type 2 diabetes mellitus, hypertension and CVD. They did and do suffer numerous nutritional deficiencies specifically; hypoglycaemia, pernicious anemia, iron deficiency, sarcopaenia and osteoporosis. The first component of the gastrectomy was a vagotomy and the second was a gastrectomy or partial gastrectomy.

These operations fell out of favour but with the **pandemic rise in obesity** rates and the limited options of treatment available and the poor outcomes of medical therapies, a new variation of the surgery was born called **BARIATRIC SURGERY**, which is now also termed **CARDIO-METABOLIC SURGERY**.

Bariatric surgery can reduce the **risk of long-term cardiovascular disease** outcomes even in the elderly (>65 years of age). Patients who underwent bariatric surgery had a 37 % lower all-cause mortality and were significantly less likely to have admissions for new-onset heart failure (64 % risk reduction), myocardial infarction (37 % risk reduction), and ischemic stroke (29 % risk reduction) as compared with similar patients who received more conservative treatment, after a median of 4 years of follow-up. (Amgad Mentias Dr. *The Journal of the American College of Cardiology*, March 2022.)



Until recently with the use of higher doses of GLP-1 agonists and combination therapy such as Phentermine and Topiramate, bariatric was the only modality that provided a significant and sustained weight loss for morbidly obese patients. Now that patients can lose >15 % of their weight, there is the resultant improvement in obesity-related comorbidities especially, type 2 diabetes mellitus, obstructive sleep apnoea, cardiovascular disease (4 point MACE), heart failure, arthritis, hypertension and malignancies.

In 1954, Kremen and Linner introduced **jejunio-ileal bypass**, the first effective surgery for obesity in the United States. In this procedure, the proximal jejunum was connected directly to the distal ileum, bypassing 90% of the small intestine out of the intestinal stream of ingested nutrients (blind loop). The procedure induced a state of malabsorption, which led to significant weight loss. This is the same as short bowel syndrome with major side effects of starvation. This created in the public and even in the medical fraternity mind that bariatric surgery is bad and that people who fail every option, choose this form of therapy as a quick fix. Many people have this **stigma** and are secretive about their operations.

All surgery has complications (CD criteria) and because morbidly obese patients have numerous co-morbidities they are at higher risk. There is also the fact that due to abnormal excessive adipose tissue, lipophilic anesthetic agents are poorly distributed and even the mechanics of ventilation are challenging. There is a fatal operative risk of 0.5 % and acute post-operative risks in 10 % which include DVT, pulmonary emboli, MI, sepsis, hemorrhage, wound dehiscence etc.



Long term follow up of patients must be life-long, as patients have the chronic complications secondary to malabsorption such as steatorrhea, diarrhea, vitamin deficiencies, oxalosis, and gout. There is also toxic overgrowth of bacteria in the bypassed intestine with resultant liver failure, severe arthritis, skin rashes.

We now have 3 basic concepts for bariatric surgery:

1. **GASTRIC RESTRICTION** (adjustable gastric banding, sleeve gastrectomy)
2. **GASTRIC RESTRICTION WITH MILD MALABSORPTION** (Roux-en-Y gastric bypass)
3. Combination of mild gastric **RESTRICTION AND MALABSORPTION** (pancreatobiliary switch).

When measuring surgical success, we must not only look at the **amount of weight loss** there is from the surgery, but also at the **improved outcomes** of the co-morbidities:

1. **Cardiovascular** (hypertension, ischaemic heart disease and peripheral vascular disease and cerebral vascular accidents, peripheral venous insufficiency, thrombophlebitis, pulmonary embolism)
2. **Respiratory** (asthma, obstructive sleep apnoea, obesity-hypoventilation syndrome)
3. **Metabolic** (type 2 diabetes, impaired glucose tolerance, hyperlipidemia)
4. **Musculoskeletal** (back strain; disc disease; weight-bearing osteoarthritis of the hips, knees, ankles, and feet)
5. **Gastrointestinal** (cholelithiasis, gastro-oesophageal reflux disease, nonalcoholic fatty liver disease, hepatic cirrhosis, hepatic carcinoma, colorectal carcinoma)
6. **Urologic** (stress incontinence)
7. **Endocrine and reproductive** (polycystic ovarian syndrome, increased risk of pregnancy and fetal abnormalities, male hypogonadism)
8. **Cancer** of the endometrium, breast, ovary, prostate, and pancreas
9. **Dermatologic** (intertriginous dermatitis, staphylococcal carbuncles, acne)
10. **Neurological** (pseudo-tumor cerebri, carpal tunnel syndrome, lumbar spine impingement)
11. **Psychological** (depression, eating disorders, body image disturbance).

Often surgery is considered as the treatment of last resort, when all else fails after dieting, exercise, sleep, cognitive behavioural therapy and drug treatments. There are certain guidelines now in place because earlier surgery has **benefits in reversing** type 2 diabetes mellitus, sleep apnoea, cardiovascular disease and even certain malignancies and arthritides.

In 1991 **National Institutes of Health** (NIH) consensus stated that the criteria for surgical treatment include:

1. Body mass index (BMI) higher than 40 kg/m^2
2. BMI higher than 35 kg/m^2 in combination with high-risk comorbid conditions, such as sleep apnoea, Pickwickian syndrome, diabetes mellitus, or degenerative joint disease
3. A new indication for bariatric surgery is to **decrease the grade of steatosis**, hepatic inflammation, and fibrosis in NAFLD.



TYPES OF PROCEDURES

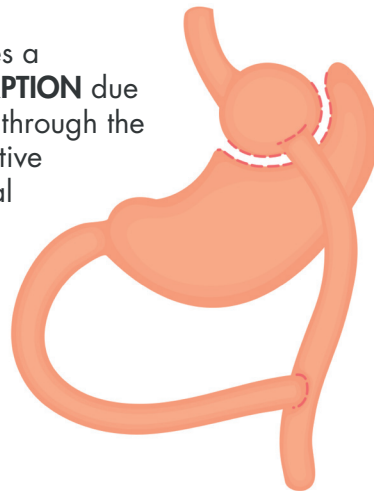


1. GASTRIC BYPASS (THE GOLD STANDARD) ROUX-EN-Y

Weight loss following a gastric bypass is due to a substantial amount of dietary **RESTRICTION**. The restriction is created by the small stomach pouch, which gives the patient a feeling of satiety after eating a small meal. The restrictive element of the operation consists of the creation of a small gastric pouch (approximately 20 mL in volume) and probably a small outlet that, on distention by food, causes the sensation of satiety. This is the same as the weight loss that is found in GLP-1 agonists (liraglutide and semaglutide). Some people have suggested that the L cells of the gut now produce 100 x more GLP-1 and -2 than before the surgery and that the incretin effect is enhanced.

A Roux-en-Y gastric bypass also provides a small-to-moderate degree of **MALABSORPTION** due to the separation of food, which passes through the alimentary limb of the Y. The malabsorptive element is a result of bypassing the distal stomach, the entire duodenum, and varying the **length of the jejunum**.

The extent of the bypass of the intestine determines the degree of macronutrient malabsorption. **The standard Roux limb is about 75 cm**. More extensive malabsorptive variations consist of gastric bypasses with a **150 cm Roux limb (long-limb)** or with a very **long-limb of greater than 150cm (distal gastric bypass)**.



ROUX-EN-Y GASTRIC BYPASS

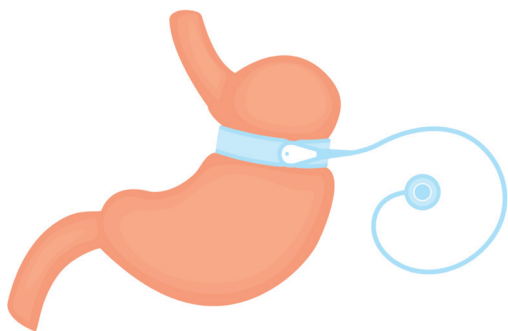
This malabsorptive element can cause a **dumping syndrome** in response to a high-sugar liquid meal. So, despite having had an operation, patients must still follow a strict low carbohydrate intake <50-100 g and no sugary drinks are allowed post-surgery. The presence of concentrated simple sugars in the Roux limb presents a substantial osmotic load that may result in cramping and abdominal discomfort and a **watery diarrhea**. There is also a rapid release of insulin by the pancreas that may cause symptomatic **hypoglycemia**. This unpleasant **Whipple's reaction** to sugar is considered to be a desired effect of gastric bypass surgery, and it has been referred to by patients as the "**postoperative police officer**". The implant of the Y must be at least within **100 cm** from the appendix/caecum of the **distal ileum** to prevent essential malabsorption, especially of vitamin B12 and iron.

Weight loss after a standard 75 cm Roux gastric bypass usually exceeds about 65-70 % of excess body weight and about 35 % drop in the BMI. The longer-limb bypasses are used to obtain comparable weight reductions in patients who are super obese (BMI >50 kg/m²). Weight loss generally levels off in 1-2 years, and after 2 years there is some weight regain but this is less than 10 kg.

For all bariatric procedures, pure **REVERSAL** without conversion to another bariatric procedure will almost certainly cause a return of the weight back to morbid obesity. Gastric bypass can be reversed, though this is rarely required. In **REVISION**, when a standard Roux gastric bypass (<75 cm) failed to lose weight, a revised operation to a very-long-limb Roux-en-Y procedure (>150 cm) can be done.

Looking at **RESULTS** long-term, follow-up postoperative success is defined as a **reduction in weight to a BMI of less than 35 kg/m²**. Strangely the patient at that BMI is still defined as obese! By this criterion, a successful outcome is achieved **in 90 % of patients** with an initial BMI of less than 50 kg/m² and **in 60 % of patients** with an initial BMI of greater than 50 kg/m².

2. LAPAROSCOPIC ADJUSTABLE GASTRIC BANDING



ADJUSTABLE GASTRIC BANDING

Laparoscopic adjustable gastric banding is the more common bariatric procedure as it is less invasive, less expensive and reversible. There are two devices: the Lap-Band and the Realize Band. This procedure is purely restrictive where an adjustable inflatable band is placed around the proximal part of the stomach. This creates a small gastric pouch (~15 mL in volume) and a small stoma.

Band restriction is adjustable by adding or removing saline from the inflatable band by a reservoir system of saline attached to the band and accessible through a port, which is attached by a catheter to the band. The port is placed subcutaneously in the anterior abdominal wall after the band is secured around the stomach.

Adjustment of the band through the access port is an essential part and is performed at least **six times** annually. Patients must chew food thoroughly to allow food to pass through the band. Adjusting the inflation of the cuff changes the size of the opening through which food passes, but does not change the size of the gastric pouch; deflation of the cuff is useful when the outlet is obstructed.

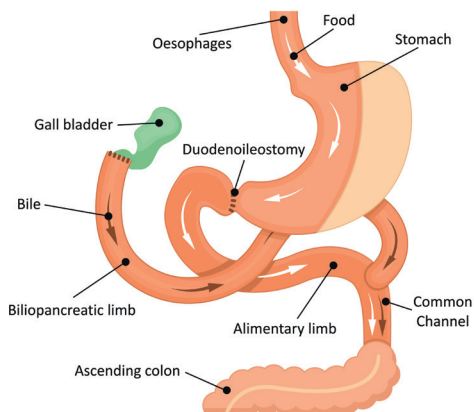
Weight loss after laparoscopic adjustable gastric banding is about **50-60 % of excess body weight** in approximately 2 years. This is often the choice of procedure in **adolescence** or in female patients in fertile years or in people unable to undergo extensive surgery.

Laparoscopic adjustable gastric banding can be **completely reversed** with removal of the band, tubing, and port.

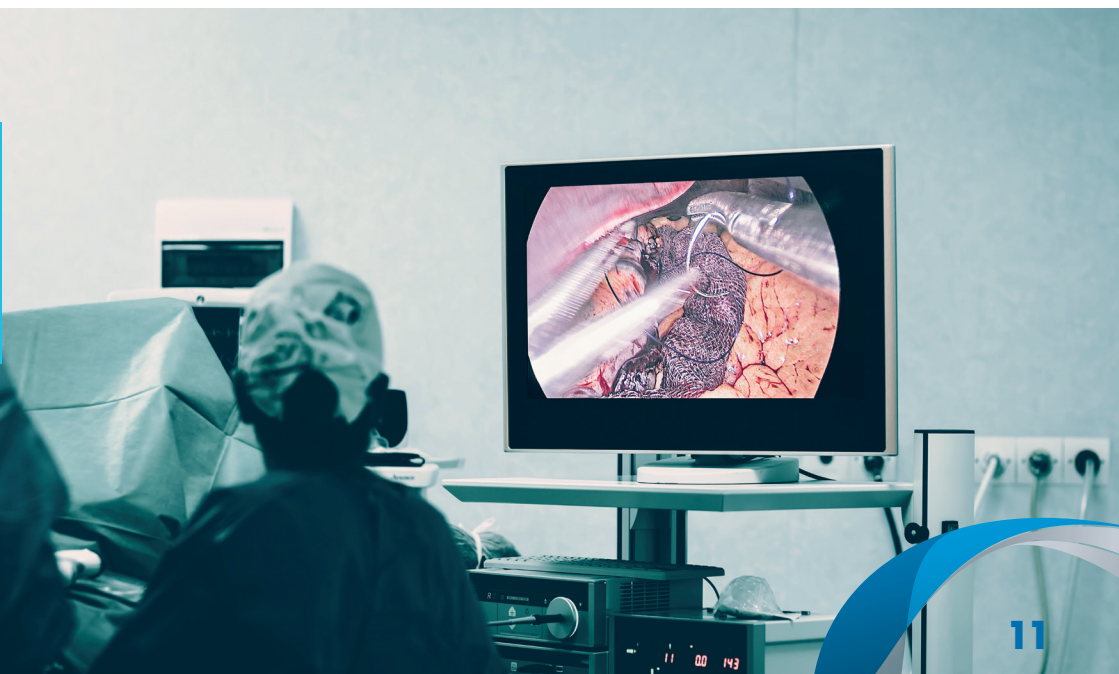
3. BILIOPANCREATIC DIVERSION WITH DUODENAL SWITCH

This is a more complicated procedure where there is a **RESTRICTIVE 75 %** gastrectomy, resulting in a tubular stomach and the duodenum is divided past the pyloric valve. The ileum is divided and the distal end is anastomosed to proximal duodenum. An optional appendectomy and cholecystectomy is often considered.

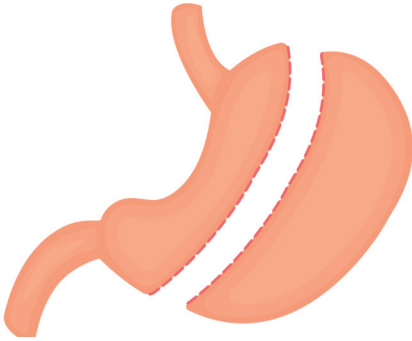
MALABSORPTION is achieved by separating food from bilio-pancreatic digestive fluids. More weight loss results from fat maldigestion and malabsorption but protein absorption is also reduced. This has the best weight loss with the least regain. There is less disruption of eating patterns with much less dumping hypoglycaemia. The results show 75-85 % of excess body weight loss at 18 months. The procedure is technically challenging, a longer operation, more expensive and difficult to reverse. The danger is a protein losing enteropathy!



BILIOPANCREATIC DIVERSION WITH DUODENAL SWITCH



4. LAPAROSCOPIC SLEEVE GASTRECTOMY



VERTICAL SLEEVE GASTRECTOMY

Laparoscopic sleeve gastrectomy (LSG), a type of unbanded gastroplasty with a subtotal gastric resection. If it is combined with a vagotomy it mimics the old Billroth gastrectomies.

In this procedure, the stomach is reduced to about 15-20 % of its original size by the surgical removal of a large portion of the stomach, following the greater curve.

The mechanism of weight loss and resultant comorbidity improvement that follows sleeve gastrectomy may be related to gastric **RESTRICTION** or to neuro-humoral changes observed following the procedure. In the follow-up period of 6 months to 3 years, patients would have lost 33-83 % of their excess weight. A gastrectomy is more physiological and there is no malabsorption.

The procedure has better outcomes than the adjustable gastric banding, but it is less effective than the Roux-en-Y gastric bypass.

The main complication is gastric **dissection line leaks** and the standard is now staple line reinforcement. In the long term (7 years and beyond) 25-35 % of LSG patients may require a revision due to full regain of lost weight.

After any bariatric type of procedure all patients must have strict **POSTOPERATIVE CARE:**

1. Patients must remain on a **high-protein, low-fat diet, low carbohydrate diet.**
2. **Supplementation** is essential Vitamin B12 injections, iron, magnesium, vitamin D3, and calcium, usually twice a day.

3. If they did not undergo an elective cholecystectomy then **Ursodiol** may be given to minimise the risk of developing gallstones during the period of acute weight loss.
4. Patients must modify their eating habits to **mechanically softer** foods.
5. **Blood tests must** be performed on a frequent basis: Full Blood Count, Calcium, Vitamin D levels, HbA1c, renal and liver function, amylase/lipase, iron studies.
6. **Body contouring** is often considered due to excessive skin only after 18 months post-surgery. Procedures such as abdomino-plasty, buttock lift, lower body lift, thigh lift, upper arm lift, facelift, breast reduction, mastopexy, and breast augmentation.

The term **METABOLIC SURGERY** came about due to reduction and reversal of type 2 diabetes mellitus. In fact, there was a reversal of all **5 factors of the cardio-metabolic syndrome**: abdominal fat, BMI, hypertension, type dyslipidaemia and overall cardiovascular risk.

In June 2016, the 2nd Diabetes Surgery Summit (DSS-II), an international consensus conference, issued the following global guidelines regarding the benefits and limitations of bariatric/metabolic surgery for type 2 diabetes mellitus:

1. Metabolic surgery should be a recommended option to treat type 2 diabetes mellitus in all patients with **>/class III obesity (BMI ≥ 40 kg/m²)**, regardless of the level of glycemic control or complexity of glucose-lowering regimens.
2. In patients with **class II obesity (BMI 35.0-39.9 kg/m²) with inadequately controlled** hyperglycemia despite lifestyle and optimal medical therapy.
3. Metabolic surgery should also be considered to be an option to treat type 2 diabetes in patients with **class I obesity (BMI 30.0-34.9 kg/m²)** and inadequately controlled hyperglycemia despite optimal medical treatment by either oral or injectable medications (including insulin).
4. Patients of Asian descent, the BMI values above should be **reduced by 2.5 kg/m²**!

Metabolic surgery is a **cost-effective treatment option** in obese patients with type 2 diabetes with an 85 % "cure" rate.

Now in our time of the **TRIPLE PANDEMIC** of obesity, type 2 diabetes mellitus and COVID-19 infection the question arose:

“Can bariatric surgery reduce COVID-19 severity and save lives?”

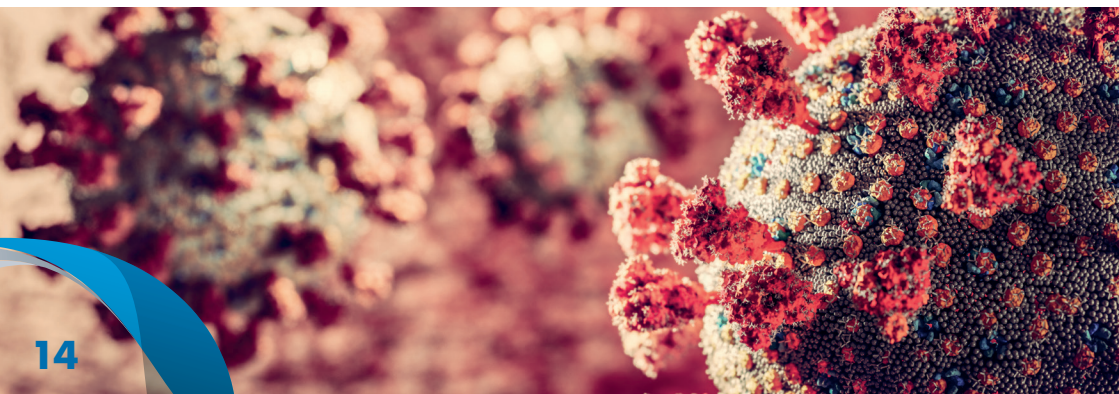
In his paper entitled ***Can Bariatric Surgery Reduce COVID-19 Severity?*** Mitchel L. Zoler, 23/02/2022 states that patients with obesity, bariatric surgery may cause substantial, durable weight loss; improved cardio-metabolic risk factors; survival benefit; and amelioration of obesity-related inflammatory state. Obesity is linked to poor COVID-19 clinical outcomes.

In his observational retrospective review of nearly 12,000 patients from a single US center, he showed that people with obesity who underwent metabolic surgery lost, on average, nearly 20 % more body weight than did matched control individuals with obesity who did not have surgery during their follow-up of almost 8 years.

Among the nearly 800 people from the study group who developed COVID-19 during the first year of the pandemic, individuals who underwent metabolic surgery had a 50% lower risk for hospitalisation, a 65 % reduced risk for the need for supplemental oxygen, and a 60 % lower risk for “severe” COVID-19 when compared with the control group. All-cause death alone was 75% lower among the people who had surgery,

His conclusion was that ***“Obesity Is a Modifiable Risk Factor for Severe COVID-19”*** and that all the guidelines should include COVID-19 to the long list of obesity comorbidities that can be mitigated by metabolic surgery.

Surgically induced weight loss favorably affects the pro-inflammatory and pro-thrombotic risks of both diseases. This change in pro-inflammation immunity reduces the CRP, TNF and Il-6 and Il-1 . There is less of a cytokine storm.



NEW DEVELOPMENTS



En par with the immune response theory, the use of a low dose once a week cortisone like Medrol 4 mg was associated with weight loss as it reduced macrophage M2 activity and reduced CRP and increased adiponectin levels.

There is marked immune dysregulation caused by obesity.

Pioglitazone

In March 2022 a study was published stating that ***“Obesity altered the immune system response to immunotherapy for allergies and asthma”***. published in *Nature*, by Dr. Ronald Evans of The Salk Institute for Biological Studies.

It was shown that patients who take peroxisome proliferator-activated receptor-gamma (PPAR-g) therapy for insulin resistance (pioglitazone), to see if there was a lower incidence for atopic dermatitis (AD). PPAR gamma allows the formation of adipocytes from pre-adipocytes and is often associated with hypertension and hypothyroidism.

In obesity there is a conversion of the classical type 2 T helper (TH2)-predominant disease associated with atopic dermatitis to a more severe disease with prominent TH17 inflammation. **Psoriasis** is a Th17-mediated disorder that is strongly associated with obesity and metabolic syndrome. Treating the obese patient with **pioglitazone** the skin improved and their molecular profile switched from TH17 back to TH2.



Gut microbiome

Immunity and specifically auto-immune disease has been linked to dysbiosis of the **GUT MICROBIOME**. In March 2022, literature published in Diabetes Care showed that **six key bacterial species** of the gut microbiome were identified as predictors of the development of type 2 diabetes in obesity. This was a large, long 15-year follow-up study of more than 5,000 people in Finland.

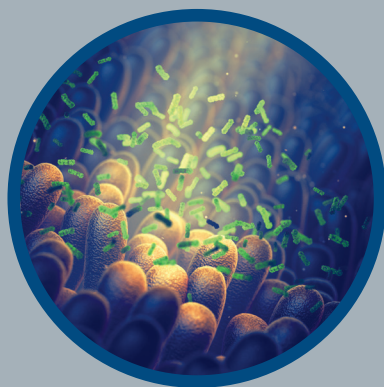
There is a strong link between dietary habits, metabolic diseases obesity and type 2 diabetes that are all modulated by the gut microbiome. The findings are from a prospective study of data on faecal samples from 5 572 people in Finland in 2002 in the FINRISK 2002 population cohort. In 2017, the samples were sent for sequencing as follow-up.

Over a median follow-up of 15.8 years, 432 (7.8 %) participants went on to have a diagnosis of type 2 diabetes, and the presence of four species and two clusters at baseline were significantly associated with the development of type 2 diabetes mellitus and fatty liver disease.

The four species include:

1. *Clostridium citroniae*
2. *Clostridium bolteae*
3. *Tyzzzeria nexilis*
4. *Ruminococcus gnavus*

The two positively associated clusters mostly consisted of the same species.



C. citroniae has been associated with trimethylamine N-oxide (**TMAO**), a compound likely linked to the intake of red meat and for years we know that there is a direct association between red meat intake and type 2 diabetes.

TMAO has also been associated with **adipose tissue inflammation** and impeded **hepatic** insulin signaling, which are all involved in increased insulin resistance, high blood glucose levels, and type 2 diabetes.

R. gnavus has been previously associated with obesity in humans and animals and this bacterial species is also related to glucose metabolism regulation and linked to increases in inflammatory cytokines, both of which are related to type 2 diabetes pathophysiology.

Linked to the prevention rather than the development of diabetes are bacterial species that help produce **butyrate**, a short-chain fatty acid. Efforts to improve insulin sensitivity via the gut through faecal microbial transplantation with an oral capsule formulation has shown benefit among patients with severe obesity. **Fibre supplementation** significantly improves insulin sensitivity among those with severe obesity and metabolic syndrome. The best fibre is fermentable fibre in the form of beans and inulin.

The good bacteria include the oligosaccharide consumers *Akkermansia muciniphila* and *Bifidobacterium infantis*, the butyrate producers *Anaerobutyricum hallii*, *Clostridium beijerinckii*, and *Clostridium butyricum*.

Microbiome modulation with faecal microbial transplant with fibre supplementations within 6 weeks can change insulin sensitivity. There is a post prandial reduction in glucose levels of 1.3 mmol/l and a HbA1c reduction of 0.8 %!

Published in Neuroscience, April 15, 2022 was a paper that demonstrated a direct dialog that occurs between the **BRAIN AND THE GUT MICROBIOTA**. The Hypothalamic neurons directly detect variations in bacterial activity and adapt appetite and body temperature accordingly.

NOD2 (nucleotide oligomerisation domain) receptor which is found mostly inside of immune cells. This receptor detects the presence of muropeptides in the hypothalamus. They subsequently discovered that these neurons electrical activity is suppressed when they come into contact with bacterial muropeptides from the gut. Conversely, if the NOD2 receptor is absent, these neurons are no longer suppressed by **muropeptides**. Consequently, the brain loses control of food intake and body temperature. There is gain of weight and susceptibility to developing type 2 diabetes.



BAM15 for Sarcopaenic Obesity

New treatments to combat muscle loss and prevent obesity in aging humans. **SARCOPAENIC OBESITY** is a condition that involves normal BMI with age-related muscle loss accompanied by abdominal obesity. Sarcopaenic obesity involves a decline in energy expenditure instead of excess intake of calories. Treatments that could increase energy expenditure could help combat sarcopaenic obesity.

Sarcopaenic obesity can decrease the quality of life and increase an individual's risk of hospitalisation and death. There is also a lack of treatments for this condition.

A new study has shown that a drug called **BAM15 (a mitochondrial uncoupling agent)** can prevent the loss of skeletal muscle mass and function and prevent weight gain.

The study suggests that BAM15 achieved this by reducing inflammation and improving the function of mitochondria. Chronic low-grade inflammation is a feature of both obesity and BAM15 treatment lowered markers of local inflammation in the skeletal muscle as well as systemic inflammation. Muscle wasting in age-related sarcopaenia is also associated with increased protein degradation and the accumulation of misfolded proteins.

Some food for thought:

Older Adults with Healthy Lifestyles Live Longer and Develop Less Dementia.

Dhana K *et al.* *BMJ* 2022 Apr 13.

It was shown that older people with higher oxytocin levels who do weight training and consume a high calcium/protein diet had the best long-term outcomes and less dementia.



QUESTIONS:



CASE STUDY:

60 year old male with hypertension and type 2 diabetes mellitus with sleep apnoea and prostatomegally, comes in for his annual full medical. His BP is 148/88 mmHg, pulse is 82/minute regular no oedema. Height is 1.84 cm and weight is 122 kg. His measured abdominal girth is 118 cm and neck circumference is 48 cm.

1. With regards to this patient:

- a) He has Class 1 obesity
- b) Low risk cardiovascular disease
- c) Fasting lipogram and ECG are essential further tests
- d) Low fat diet is recommended
- e) Testosterone is first line of therapy.

2. According to the guidelines this patient:

- a) Qualifies for a gastric bypass operation
- b) BMI is 32kg/m²
- c) Diabetes, hypertension and sleep apnoea need not be treated
- d) His weight will respond to a PAAR gamma agonist like pioglitazone
- e) He can have a high purine intake with a high protein diet as he is at low risk for hyperuricaemia.

3. Guidelines for bariatric surgery include:

- a) BMI of 27 kg/m² and GERD
- b) Metabolic syndrome on no medical treatment
- c) CPAP plays a vital role in therapy in sleep apnoea initially
- d) He has a 5 % potential intra-operative mortality rate
- e) No gastroscopy is needed.

4. With regards to surgery:

- a) The patient only qualifies for a laparoscopic gastric banding
- b) A Roux-en Y procedure has the potential of reversing his CPAP and diabetes mellitus
- c) There is a very high risk of heart disease after 5 years of follow up
- d) A weight loss of 12 kg is expected
- e) The patient is too old and will not benefit from surgery.

5. You suggest a new diet for this patient post-surgery:

- a) A diet high in beans, fibre and fermented foods
- b) High protein especially red meat intake
- c) No need for supplementation as his diet is sufficient
- d) No exercise needed as operation will cause weight loss and offer cardiovascular protection alone
- e) High glucose intake is essential to prevent hypoglycaemia.

6. The use of a GLP-1 agonist:

- a) Is of no use in this patient if he already is using oral anti-diabetic medication
- b) Could reverse his potential fatty liver disease
- c) Should not be prescribed post operatively to this patient
- d) Gall bladder disease is not significant
- e) Contra-indicated to use in uncontrolled hypertension and ischaemic heart disease.

7. If the patients develops painful joints:

- a) Stop any statin therapy as this causing the arthritis
- b) He could possibly have psoriasis with Th17 expression
- c) There is a low risk of gout
- d) High calcium intake is needed to prevent the bone pains
- e) Thiazide diuretics are first choice as antihypertensive.

8. Immune dysregulation in this patient:

- a) He has high adiponectin levels
- b) High macrophage M2 activity with raised CRP
- c) He has a low risk for severe COVID-19 infection
- d) IL-6 is low
- e) His gut bacteria will have high butyrate levels.

9. With regards to Gut bacteria:

- a) A high concentration of *clostridium difficile* is beneficial
- b) Antibiotics should be used to treat all gut symptoms to prevent bacterial overgrowth
- c) Ulcerative colitis can be treated by a faecal transplant
- d) Post COVID-19 infection shows a high diversity of gut flora
- e) No change is seen in gut microbiome after gastric bypass operations.

10. Lifestyle changes when over 60 years of age:

- a) Play no role in disease outcomes
- b) Cause muscle atrophy
- c) Increase insulin resistance
- d) Cause protein clumping and poor mitochondrial uncoupling
- e) Reduce risk of cognitive decline significantly.



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