ESE Clinical Update on Obesity 2021

A series of webinars held on 29 November – 1 December 2021
Welcome

The increasing prevalence of obesity in Western societies provides us with a developing challenge. This report presents the content of three dynamic webinars that examined our latest understanding of hormones in obesity, both as the cause and the effect of the disease. Consideration was given to obesity’s diagnosis, management and the future of this field of medicine.

The European Society of Endocrinology (ESE) was delighted to welcome experts in the field of obesity, who shared their knowledge and experience during three, 2-hour webinar sessions that considered:

• aspects relating to diagnosis, such as the disease’s pathogenesis, a patient’s perspective, obesity’s relationship with endocrine disorders, the use of metreleptin in anorexia nervosa and approaches to anti-obesity pharmacotherapy

• the management and challenges of obesity, including an increased susceptibility to infectious disease, the complications of weight regain or hypoglycaemia after bariatric surgery, and avoidance of nutritional deficiencies

• treatment and the future landscape, which looked at our current understanding of adipose tissue biology, the genetics of obesity in the context of precision medicine, and pharmacotherapy and multimodal conservative treatment.

We are grateful to all who took part, including the attendees, who contributed important experience and many pertinent and relevant questions.

The content of the webinars is available to attendees at www.eseondemand.org.

Uberto Pagotto, Liesbeth van Rossum, Volkan Yumuk, Gema Frühbeck and Peter Kühnen
Scientific Programme Committee

Kindly supported by Novo Nordisk and Medtronic
## Contents

### Welcome

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>02</td>
</tr>
</tbody>
</table>

### Chairs and Speakers

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>04</td>
</tr>
</tbody>
</table>

### Webinar 1: Diagnostic dilemmas in obesity

- Drivers and pathogenesis of obesity - Arya Sharma (Canada)  
- Patient perspective: stigmatisation and the diagnostic process - Susie Birney (Ireland)  
- Improvements in anorexia nervosa with recombinant human leptin - Jochen Antel (Germany)  
- Obesity: cause or consequence of endocrine disease? Using the ESE Guideline - Mariana P Monteiro (Portugal)  
- Diagnostic dilemmas in obesity: what kinds of drugs should we (not) use? - Luc van Gaal (Belgium) 

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>05</td>
</tr>
</tbody>
</table>

### Webinar 2: Management and challenges of obesity

- Obesity and infections - Manel Puig Domingo (Spain)  
- Weight regain after bariatric surgery - Rachel Batterham (UK)  
- Hypoglycaemia after bariatric surgery - André van Beek (The Netherlands)  
- Management of nutritional deficiencies - Stephan Bischoff (Germany) 

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
</tr>
</tbody>
</table>

### Webinar 3: Treatments and future landscape

- Latest developments in adipose tissue biology - Karine Clément (France)  
- The genetics of common obesity in the era of precision medicine - Ruth Loos (Denmark)  
- Pharmacotherapy and multimodal conservative treatment - Roberto Vettor (Italy) 

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Page</th>
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</thead>
<tbody>
<tr>
<td>19</td>
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Chairs and Speakers

ESE thanks all faculty members for their valuable contributions to the ESE Clinical Update on Obesity 2021.

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Diagnostic dilemmas in obesity

Chairs: Uberto Pagotto (Italy) & Liesbeth van Rossum (The Netherlands)

Drivers and pathogenesis of obesity

Arya Sharma  Edmonton, Canada

New Canadian Adult Obesity Clinical Practice Guidelines were published in 2020.1 These proposed a new approach to defining and diagnosing obesity. Obesity should be understood as a chronic, progressive, relapsing disease characterised by the presence of abnormal or excess adiposity that impairs health and social well-being. To be considered a disease, obesity must result in some impairment of health. This means that in a clinical context, body mass index (BMI) alone is insufficient to diagnose obesity. Health Canada has recommended that the diagnosis of obesity not be based on BMI alone.

Screening for obesity

Regular assessment of BMI, waist circumference and cardiometabolic risk factors can help identify people at risk of developing obesity. For most populations, a BMI of 25kg/m² or more represents an increased risk and should prompt further evaluation of other anthropometric, haemodynamic and biochemical parameters.

In some populations, individuals may have obesity at a much lower BMI. In adults with South, Southeast or East Asian ethnicity, the recommended cut-off for overweight should be a BMI of 23kg/m² or more.

BMI should also be interpreted with caution in elderly patients, very muscular patients and those with extremely tall or short stature. In elderly individuals, sarcopenic obesity has its own diagnostic challenges.

Taking BMI as the defining characteristic of obesity makes it difficult to grade severity of disease which, in turn, guides treatment decisions. Individuals may have a low BMI with multiple medical problems, while others have a high BMI and are otherwise healthy.

Edmonton Obesity Staging System

The Edmonton Obesity Staging System (EOSS) was created to address some of these challenges. It offers a measure of the mental, metabolic and physical impact of obesity on a patient’s health and has been validated in more than 50 studies. The following factors are used to determine stage of obesity on a scale of 0–4:

- stage 0 (also referred to as pre-obesity): no apparent obesity-related risk factors, no physical symptoms, no psychopathology, no functional limitations or impairment of well-being
- stage 1: presence of subclinical risk factors, mild physical symptoms, mild psychopathology, mild functional limitations and/or impairment of well-being
- stage 2: presence of obesity-related chronic disease, moderate psychopathology, moderate limitations in activities of daily living and/or well-being
- stage 3: established end-organ damage, significant psychopathology, functional limitations and/or impairment of well-being
- stage 4: severe disabilities from obesity-related chronic diseases, disabling psychopathology, functional limitations and/or impairment of well-being

In population studies, the EOSS has been shown to be a better predictor of all-cause mortality when compared with BMI or waist circumference measurements alone.2

Drivers of obesity

Rates of obesity are increasing worldwide. Drivers include a complex interplay of changes in food production, activity environment, individual activity and food consumption, and cultural attitudes.3 There is emerging evidence that the microbiome may be an important factor in certain individuals.

Individuals exposed to the same environmental and cultural circumstances do not all develop obesity. Studies of twins have demonstrated that body shape and size are genetically determined. Common obesity is known to be highly genetic but, with so many genes involved, it is difficult to identify the underlying genetic cause. Evidence suggests that some cases of obesity, particularly in children, may be attributable to epigenetic changes rather than genetic changes.

Table. 4Ms framework for the assessment of obesity.4

<table>
<thead>
<tr>
<th>Mental</th>
<th>Mechanical</th>
<th>Metabolic</th>
<th>Milieu</th>
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<tbody>
<tr>
<td>Knowledge/cognition</td>
<td>Osteoarthritis</td>
<td>Type 2 diabetes</td>
<td>Socioeconomic status</td>
</tr>
<tr>
<td>Expectations</td>
<td>Sleep apnoea</td>
<td>Diabetes</td>
<td>Education</td>
</tr>
<tr>
<td>Self-image</td>
<td>Plantar fascitis</td>
<td>Hypertension</td>
<td>Occupation</td>
</tr>
<tr>
<td>Internalised weight bias</td>
<td>Gastro-oesophageal reflux disease</td>
<td>Gout</td>
<td>Access to food</td>
</tr>
<tr>
<td>Stress</td>
<td>Urinary incontinence</td>
<td>Fatty liver disease</td>
<td>Disability</td>
</tr>
<tr>
<td>Mood/anxiety</td>
<td>Intertrigo</td>
<td>Gallstones</td>
<td>Access to medication</td>
</tr>
<tr>
<td>Attention</td>
<td>Pseudotumour cerebri</td>
<td>Poly cystic ovary syndrome</td>
<td></td>
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<tr>
<td>Addiction</td>
<td>Thrombosis</td>
<td>Hypogonadism</td>
<td></td>
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<tr>
<td>Eating disorder</td>
<td></td>
<td>Infertility</td>
<td></td>
</tr>
<tr>
<td>Sleep</td>
<td></td>
<td>Coronary artery disease/</td>
<td></td>
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<tr>
<td>Personality</td>
<td></td>
<td>congestive heart failure/</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>atrial fibrillation</td>
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<td></td>
<td></td>
<td>Cancer</td>
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The brain’s role in controlling ingestive behaviour
Most obesity is a consequence of consuming more calories than the body needs. Therefore, it makes sense to consider behavioural interventions that target the causes of over-eating (or insufficient energy expenditure). However, relying on executive function alone to change obesity-causing behaviours is unlikely to be successful.

The brain drives eating behaviour in three ways: homeostatic eating (eating for hunger), hedonic eating (eating for pleasure) and executive function (deciding to eat), as shown in the Figure on page 5. The homeostatic centre works to maintain energy balance and prevent weight loss, in response to multiple hormonal and neuroendocrine signals that indicate satiety and hunger. This system counter-regulates dieting behaviour to prevent excessive weight loss, which can make long term weight loss very challenging. The hedonic centre regulates motivation to eat and pleasure from eating through dopamine, cannabinoid and opioid receptors. These systems are not within conscious control, yet that is what education-based obesity management is attempting. This is why sustained long term weight loss results are so rare.

4Ms framework for assessing obesity
The Canadian guidelines suggest a framework for assessing obesity based on understanding the causes and consequences of obesity for an individual. Assessment of treatment options should identify barriers that might inhibit likelihood of success. The framework is broken down into four steps, known as the ‘4Ms’: mental health, mechanical issues, metabolic consequences and the patient’s social milieu.

Possible drivers of obesity and barriers to weight loss under each category are shown in the Table on page 5.

A review of the patient’s medication history for both obesogenic medications and anti-obesity medications should be considered. Determining when obesity started can also indicate what might be driving obesity in individuals.

Obesity management model
Treatment is broken into three phases: weight stabilisation, weight loss and weight loss maintenance. The final phase is the most challenging. Understanding the drivers of obesity for the patient is important in all phases.

The usual ‘pyramid’ model of obesity management encompasses lifestyle, dietician support and medication, followed by surgery if those interventions don’t work. The Canadian guidelines offer a different model, focusing on a foundation of nutrition treatment and physical activity, supported by psychological support, pharmacotherapy and/or bariatric surgery, depending on the patient’s needs.

More research is needed to determine which treatments are most effective for different aetiologies. It is worth investigating the causes of obesity, regardless of the treatment option that is pursued.

REFERENCES

Patient perspective: stigmatisation and the diagnostic process
Susie Birney Dublin, Ireland

People living with obesity experience many types of stigma, including from healthcare professionals. To show how weight stigma affects my life, I’ll share my experience of going to hospital for a kidney test 20 years ago.

A day in the life
In the morning, I took the bus to the hospital. No one would sit beside me. At the hospital, a nurse asked me to provide a urine sample, but I couldn’t fit in the nearest cubicle. I had to walk to find a wheelchair-accessible toilet, and the nurse was visibly annoyed at the delay. The blood pressure cuff didn’t fit me, and the nurse said, ‘Your fat is in the way. We can’t really do this test. It’s obvious you didn’t fast last night.’ She told me I was non-compliant, even though I’d fasted since 6pm the night before. I had to leave with the test unfinished.

At this stage, I’d been fasting for quite a long time. I don’t have many options with avoidant restrictive food intake disorder, so I went to the nearest fast-food outlet and ordered a hamburger and a bottle of water. A man said, ‘Do you really need to eat that?’ I walked out without eating. Again, no one would sit next to me on the bus home. I felt broken. I couldn’t talk to family and withdrew into myself.

Stigma prevents at-risk patients from seeking care
I didn’t reschedule the appointment. I couldn’t face going back. This is what stigma does: it stops people living with obesity from getting the care they need.

I was eventually referred to the weight management service because of my diabetes, when I was diagnosed with diabetic retinopathy. But didn’t I need that intervention years earlier? I believe it’s a form of stigma not to diagnose or treat obesity in a timely manner, as with any other chronic, relapsing disease.

For years, I put living on hold. I received stigma from family. I put off holidays and job interviews. I decided to start living again after going to a rock concert and realising that weighing less wouldn’t make the experience any better.

Discussion
Research suggests that 80% of Dutch patients with obesity avoid visiting the doctor because of stigma. Another study revealed that 55% of physiotherapy students in Ireland felt working with people with obesity was a waste of time. In response, the Irish Coalition for People Living with Obesity established a committee alongside the Association for Studies of Obesity Ireland, to work towards adding obesity stigma education to the curriculum for ALL healthcare students in Ireland.

Doctors can help by making small changes to their language. Say ‘people with obesity’, as you would with other diseases, instead of ‘obese people’. Ask permission to discuss weight. Listen to the patient’s story and don’t assume that a patient hasn’t tried to lose weight before. Having the right equipment to accommodate larger bodies will also make a difference.
Improvements in anorexia nervosa with recombinant human leptin

Jochen Antel Essen, Germany

The adipokine leptin is of interest to researchers of both obesity and anorexia nervosa (AN), because of its role in regulating appetite, metabolism and energy homeostasis. Leptin deficiency is associated with starvation or AN, while leptin resistance is associated with obesity.

Leptin mediates resistance to obesity by increasing in response to a positive energy balance. Studies in mice and humans in the early 2000s showed that long term application of recombinant leptin promotes weight loss in lean-to-normal-weight subjects, but less so in those with obesity. This suggests that leptin is probably a major signal for adaptation to starvation.

Short term starvation causes reduced energy expenditure but, paradoxically, can also induce liveliness. Increased physical activity can also be a crucial adaptation in prolonged starvation, to allow for flight or to procure food. Since this hyperactivity is associated with low leptin levels, researchers hypothesised that leptin treatment could alleviate restlessness and potentially other starvation-related symptoms in people with AN.1

AN symptomatology and treatment

More women than men experience AN, with a ratio of 10:1. Lifetime prevalence is 0.5–2%. The core symptomatology is an intertwining of primary cognitions and behaviours with somatic and psychological consequences of starvation. Typically, there is a fear of gaining weight, persistent behaviour that interferes with weight gain, and body image disorder.

Many psychological symptoms overlap with the effects seen in the Minnesota starvation experiment, a 1944–1945 study of adaptations to starvation in 36 voluntary participants. In response to 24 weeks of starvation, participants experienced tiredness, depressed mood, increased rigidity, reduced social ability, reduced concentration, restlessness and reduced spontaneity.

Treatment for AN usually includes psychoeducation, psychotherapy and re-alimentation. Currently there is no approved pharmacotherapy. There are several off-label treatments, mostly with antipsychotics, but the success rate is extremely low. Mean disease duration is about 3.5 years, plus the same again with other eating disorders. It is the psychiatric disorder with the highest mortality rate.

Metreleptin as a treatment for AN

In acute AN, there is a clear correlation between adipokine leptin levels and body mass index during weight recovery and relapse.2

An animal study in the early 2000s found that starvation-induced hyperactivity could be counteracted with leptin treatment. This led to consideration of leptin as a possible treatment for AN. The recombinant human leptin metreleptin has been used in more than 30 clinical trials since 2001. It was granted approval by the US Food and Drug Administration for generalised lipodystrophy in 2014, and by the European Medicines Agency for generalised and treatment-resistant partial lipodystrophy in 2018. Metreleptin has not been permitted for use in eating disorder trials, so an investigator-initiated clinical trial is needed to test the medical hypothesis that leptin could be a treatment for AN.

To date, about 10 patients (nine females and one male) have been included in case studies across four hospitals. Treatment included the standard combination of an eating plan, psychotherapy and occasional medication, depending on the patient. Patients were given 3–10mg metreleptin/day, for 6–24 days (80 days for the male patient), and results recorded using self-reporting frameworks and clinician observations.

The research team expected to see an impact on hyperactivity and possibly additional benefits in mood and eating disorder-specific cognition. The results showed a rapid onset of strong beneficial effects, including improved sleep, reduced inattention and reduced urge to move. There were clear antidepressant effects, improved social interaction and reduced fear of weight gain. Patients even experienced increased appetite and hunger. No adverse events were observed.1

The Figure on the left shows the effect of leptin for one patient. The effect lessened once leptin was no longer administered, though repetitive thoughts of food, fear of weight gain, inner tension and depressive mood all remained lower than at baseline.

The results showed a rapid onset of strong beneficial effects, including improved sleep, reduced inattention and reduced urge to move. There were clear antidepressant effects, improved social interaction and reduced fear of weight gain.1

Figure. Effects of short term metreleptin treatment in a patient, showing means of six key cognitions and emotions assessed three times per day with visual analogue scales (range 1–10). Reproduced under CC BY 4.0 licence (https://creativecommons.org/licenses/by/4.0) from Milos et al.1 https://doi.org/10.1038/s41398-020-00977-1 ©2020 The Authors.
Standard antidepressants are ineffective in patients with AN. However, metreleptin resulted in a very strong effect within a short time frame, as demonstrated for another patient. This patient’s parents also reported significant improvements in his well-being.

**Is AN a hormone deficiency disorder?**

These findings suggest that AN might be a type of hormone deficiency disorder, perhaps related in part to a deficiency in leptin.

The leptin substitute appears to take effect in just 14 days. First, the patient’s mood and social interactions seem to improve. Then, there is a reduction in weight phobia and food, rigidity and compulsiveness. Finally, there is a reduction in preoccupation with weight loss, these dysfunctions often regress. The effect is somewhat counterintuitive, as leptin is understood to promote an anorexigenic effect. The appetite-reducing effect seen here is most likely to result from the patient no longer feeling trapped by the need to stay slim. By reducing the preoccupation with avoiding weight gain, leptin allows the natural appetite to return.

To garner results beyond single case observations, a placebo-controlled, multicentre, randomised, double-blind, dose-ranging parallel study is planned, to investigate the antidepressant efficacy and safety of metreleptin over 3 weeks. The study will include 40 patients in the treatment group and 40 patients in the control group.

**Conclusions**

Preoccupation with food is an overarching phenotype in congenital leptin deficiency, generalised lipodystrophy and AN.

**Obesity: cause or consequence of endocrine disease? Using the ESE Guideline**

Mariana P Monteiro Porto, Portugal

Obesity can be both a cause and a consequence of many endocrine disorders. Understanding the direction of causation is important to determine the most appropriate treatment.

Endocrine disorders that contribute to obesity include androgen deficiency in men, androgen excess in women and drug-induced endocrine dysfunction, as shown in Table 1 on page 9. Less common examples are Cushing’s disease, hypopituitarism and growth hormone deficiency. Conversely, obesity can trigger numerous hormonal alterations, affecting thyrotrophin (TSH), adrenal function, growth hormone, sex steroid hormones and vitamin D. Table 2 on page 9 shows some examples of hormonal fluctuations in obesity. Following significant weight loss, these dysfunctions often regress without any further intervention. In these cases, addressing obesity can improve hormonal dysfunction, while addressing the biochemical alterations would not necessarily result in successful obesity management. Therefore, treating obesity should be the priority for most patients.

**Clinical practice guideline development**

The panel that developed the recent ESE Clinical Practice Guideline on endocrine work-up in obesity conducted a systematic review and meta-analysis of the literature before issuing recommendations. They made use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, which takes into account quality of evidence, the balance of desirable and undesirable outcomes, values and preferences, and the clinical experience of the panel. A distinction was made between strong ‘recommendations’ and ‘suggestions’.

**Obesity and hypothyroidism**

It is recommended that all patients with obesity are tested for thyroid function. The prevalence of overt and subclinical hypothyroidism in patients with obesity is quite high, at around 14–14.6%, rising to 25% in patients who are candidates for bariatric surgery. Although progression of subclinical hypothyroidism is very slow, prevalence is considerably higher in patients with obesity than in the general population. Hypothyroidism could lead to weight gain and worsen obesity co-morbidities. Assessment is simple and treatment is safe and inexpensive.

The guideline recommends against the use of thyroid hormones to treat obesity where thyroid function is normal. There is a perception that hypothyroidism can cause weight gain and decrease energy expenditure, which has led to the popular fallacy that thyroid hormone preparations may be used as anti-obesity drugs. Treatment of hypothyroid patients with thyroxine (T4) until clinically euthyroid does not change body mass index. Therefore, thyroid hormone treatment should not be initiated based on elevated TSH levels with normal T4 alone. Weight loss is unlikely, and T4 treatment may deter the patient from seeking appropriate obesity management.

**Obesity and hypercortisolism**

It may often be assumed that people with obesity have subclinical Cushing’s syndrome due to hypercortisolism, though this is rarely the case. Fewer than 1% of patients with obesity have Cushing’s syndrome. Therefore, the guideline recommends only investigating for Cushing’s syndrome where there is a strong clinical suspicion.

Biochemical testing is recommended where there is a high suspicion of hypercortisolism, as it is more prevalent in patients with concomitant type 2 diabetes and in those with resistant hypertension.

Catabolic manifestations such as osteoporosis, wide purple striae, spontaneous ecchymosis and thin skin are associated with a 95% probability of Cushing’s syndrome. Features of Cushing’s syndrome that are also common in obesity include central obesity, type 2 diabetes, hypertension and dyslipidaemia. It is particularly important to rule out Cushing’s syndrome in candidates for bariatric surgery, to avoid complications and adverse outcomes.

**Obesity and male hypogonadism**

The guideline does not recommend routine biochemical testing for hypogonadism in male patients with obesity. Testing is only recommended where there are key signs and

**REFERENCES**

Diagnostic dilemmas in obesity

Webinar 1


Table 1. Examples of some endocrine disorders/disturbances that cause or contribute to obesity.1

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<thead>
<tr>
<th>Condition</th>
<th>Prevalence in obesity</th>
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<tr>
<td>Androgen deficiency (men)</td>
<td>Common</td>
</tr>
<tr>
<td>Androgen excess (women)</td>
<td>Common</td>
</tr>
<tr>
<td>Cushing’s disease or Cushing’s syndrome</td>
<td>Rare</td>
</tr>
<tr>
<td>Drug-induced endocrine dysfunction (e.g., lithium, anti-depressants, antipsychotics, glucocorticoids)</td>
<td>Common</td>
</tr>
<tr>
<td>Ovarian failure (premature or menopause)</td>
<td>Premature uncommon Physiological (menopause) common</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
<td>Rare</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>Rare</td>
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Table 2. Examples of some hormone alterations seen in obesity.1

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Levels in obesity</th>
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<tbody>
<tr>
<td>Thyrotrophin</td>
<td>N or ↑</td>
</tr>
<tr>
<td>Free thyroxine</td>
<td>N or slightly ↓</td>
</tr>
<tr>
<td>Cortisol (blood and urine, salivary)</td>
<td>N or ↑ Altered suppression tests</td>
</tr>
<tr>
<td>Adrenocorticotrophin</td>
<td>N or ↑</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>N or ↓</td>
</tr>
<tr>
<td>Insulin-like growth factor-1</td>
<td>N or ↓</td>
</tr>
<tr>
<td>Prolactin</td>
<td>?</td>
</tr>
<tr>
<td>Testosterone (male)</td>
<td>↓</td>
</tr>
<tr>
<td>Testosterone (female)</td>
<td>↑</td>
</tr>
<tr>
<td>Luteinising hormone/ follicle-stimulating hormone</td>
<td>↓ in men ↑ LH in women</td>
</tr>
<tr>
<td>25-OH vitamin D</td>
<td>↓</td>
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<td>Rare</td>
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</table>

Symptoms of hypogonadism. Testosterone treatment is suggested for consideration in individual cases, but not solely because a patient has obesity.

The prevalence of male hypogonadism is very high in patients with obesity. More than 40% of patients have male hypogonadism when assessed by total testosterone (TT), and more than 30% when assessed by free testosterone (FT).1 Prevalence is even higher in patients with type 2 diabetes. However, male hypogonadism can be both a cause and a consequence of obesity.

Weight loss can improve TT and FT levels, and should therefore be the first-line therapeutic approach when attempting to reverse functional male hypogonadism in patients with obesity. Testosterone replacement therapy has several positive clinical effects, but a modest effect on body mass index and lean mass. If there is no improvement in the signs and symptoms of hypogonadism after 6–12 months, testosterone should be stopped to prevent adverse side effects.

**Obesity and female hypoandrogenism**

Similarly, the guideline recommends against routine testing for hypogonadism in female patients with obesity. Assessing gonadal function is recommended in individuals experiencing menstrual irregularities and chronic anovulation or infertility. Assessing androgen levels is recommended when the clinical signs of polycystic ovary syndrome (PCOS) are present.

The rationale for these recommendations is that, while PCOS occurs in 29% of female patients with obesity, increasing to 36% in women with severe obesity,4 the prevalence of PCOS in women with obesity is similar to the general population.

**General recommendations**

Since hormonal imbalances tend to be driven by obesity, the guideline recommends that weight loss should be the priority during diagnostic assessment and emphasised as the key to restoration of hormonal balance.

The European Guideline for Obesity Management in Adults5 recommends that, when taking a medical history of patients with obesity, consideration should be given to endocrine abnormalities. Laboratory tests should include universal screening for thyroid function. Adrenal and sex steroid function should be tested according to clinical suspicion.

Biochemical tests which are considered adequate to assess endocrine dysfunction in patients with obesity are as follows:

- for hypothyroidism, raised TSH
- for male hypogonadism, TT or FT on two separate days in a fasting state
- for female hyperandrogenism, TT or FT measured at any time during the menstrual cycle
- for hypercortisolism, two or more of urine free cortisol, late-night salivary cortisol, serum cortisol after 1-mg overnight dexamethasone suppression test, or low-dose dexamethasone suppression test (2mg/day for 48 hours).

More details on testing TT/FT are included in the guideline, given the challenges in taking accurate measurements for FT.

**REFERENCES**


‘Since hormonal imbalances tend to be driven by obesity, the guideline recommends that weight loss should be the priority during diagnostic assessment and emphasised as the key to restoration of hormonal balance.’
Diagnostic dilemmas in obesity: what kinds of drugs should we (not) use?

Luc van Gaal Antwerp, Belgium

Weight management in patients with obesity is challenging for several reasons. The pathophysiology of obesity is complex, patients may have multiple co-morbidities, and there can be side effects associated with some drug therapies. Patient adherence can also be inconsistent.

However, the benefits of weight loss are clear: weight loss of 5–10% can reduce the risk of type 2 diabetes, improve blood lipid profiles and blood pressure, improve liver histology, and improve quality of life.

Benefits and limitations of drug therapy
Pharmacotherapy can help more patients adhere to behaviour change programmes and increase the magnitude and duration of results.1

Unfortunately, many drugs fail during clinical development, often due to moderate to severe side effects. Clinicians should be wary of prescribing drugs containing sibutramine, which has been associated with a 16% increased risk of primary outcome events, which has been associated with a 16% increased risk of type 2 diabetes by an additional 2–7% on top of lifestyle modification.

Topiramate/phentermine is a combination therapy not available in Europe as an anti-obesity medication. However, it is available as an anti-convulsant, and has been shown to have a positive effect on weight management.

Glucagon-like peptide-1 receptor agonists
Glucagon-like peptide-1 receptor agonists (GLP1 RAs) are commonly used to treat type 2 diabetes. Liraglutide, which is taken once daily, has been studied as a potential treatment for obesity and is now available in Europe. The European Medicines Agency is expected to grant approval shortly to semaglutide, which is taken once weekly.

Liraglutide works by stimulating neurones in the hypothalamus (POMC, pro-opiomelanocortin, and CART, cocaine- and amphetamine-regulated transcript) to increase satiety, and by blocking certain neuropeptides (NPY, neuropeptide Y, and AgRP, agouti-related peptide) to reduce hunger, thus reducing overall appetite, as shown in the Figure below.2 A dose-dependent study showed patients achieved a weight loss of around 10% after taking liraglutide for 2 weeks.

The ideal approach is to start with a low-calorie diet to allow the patient to lose as much weight as possible through lifestyle modifications, and then to add the drug to increase the amount of weight lost until the treatment stops. This can take total weight loss from 6–7kg to 13–14kg.

However, because obesity is a metabolic disease, as soon as you stop the metabolic treatment, the effect will cease.3

Compared with other anti-obesity drugs such as orlistat and naltrexone/bupropion, liraglutide results in more patients achieving a weight loss of 5% or more at 12 weeks. Early responders tend to be a better predictor of 1-year outcomes.

While liraglutide is not approved for treatment of polycystic ovary syndrome (PCOS), it has been shown to have a positive effect. In one pilot study, it was shown to increase pregnancy rates for patients undergoing in vitro fertilisation who had obesity and PCOS and who responded poorly to first-line reproductive treatments.4 It has also been shown to have a positive effect in a randomised controlled trial of adolescent patients with obesity.

Clinical case study: liraglutide
Treatment options were being considered for a woman aged 38 with a long history of obesity. She had been diagnosed with PCOS, but assessments for hypothyroidism, Cushing’s disease, and kidney and liver function were all normal. She was taking medications for hypertension and epilepsy that may have been drivers of obesity. Adherence to lifestyle modifications had been challenging. Options for the next line of treatment included an oral medication such as orlistat, an injectable GLP1 RA, or bariatric surgery.

The patient started liraglutide with progressive up-titration to 3mg per day, eventually losing 10kg after 12 months. Lipid parameters improved and glucose tolerance normalised.

Future perspectives
Subcutaneous semaglutide is a promising drug which may be available in the future. A recent study showed that daily semaglutide injections reduced body mass index by 16.9% over 68 weeks, compared with 2.4% in the placebo group.5 Up to 35% of patients taking semaglutide were able to achieve more than 20% weight loss, which is closer to the results possible with surgical approaches.

Oral semaglutide has not been studied for obesity control, but appears to have a similar effect to subcutaneous semaglutide in patients with type 2 diabetes.

REFERENCES
Management and challenges of obesity

Chairs: Volkan Yumuk (Turkey) & Uberto Pagotto (Italy)

Obesity and infections

Manel Puig Domingo Barcelona, Spain

Obesity is associated with an increased susceptibility to infection. The available data suggest that people with obesity are more likely to develop postoperative and nosocomial infections than control subjects. Complications are also more likely, and when infection results in hospitalisation, obesity-related factors may lead to a longer stay and more treatment.

There is a high susceptibility to dermal infections among patients with obesity. Increased dermal fats affect the bacteria living on the skin, which can cause lesions to be more severe than in patients who do not have obesity, and can lead to cellulitis. Disruption to the immune system impairs the resolution of infections that would otherwise be of minor importance. Skin-related conditions that are common in obesity, such as lymphoedema, exacerbate this.

Obesity-related conditions in other organs influence the frequency of infection, and this risk increases with the severity of obesity. For example, there is an increased risk of respiratory tract conditions, causing decreased pulmonary volumes and sleep apnoea syndrome. Diabetes mellitus contributes to more aggressive infection in people with obesity. Impairment of the immune system, such as the altered differentiation of macrophages or dysregulated cytokine production, can have a deleterious effect and contribute to poor clinical outcomes. There are also limited data on the correct dosing of antimicrobial treatments in obesity. Levels of virtually all effector cells are disrupted in individuals with obesity.

Microbiota in people with obesity have been shown to influence lung function. Antibiotic treatments, co-morbidities and ageing can lead to dysbiosis which, in turn, causes a defective immune response in the lungs, leading to uncontrolled viral and bacterial infection.

Leptin as immune system protector

Leptin appears to have a key role in linking nutritional state to the immune response. It stimulates the immune system at the central level (thymus), regulates T cells, and activates macrophages, polymorphonuclear cells and monocytes.

In people with obesity, dysfunction or an absence of leptin can disrupt the development of the respiratory tract in a dose-dependent manner. In extreme cases, there is increased susceptibility to and mortality from respiratory tract infection. The Figure below shows how individuals with obesity who have an influenza infection can experience an increased amount and longer duration of viral shed in comparison with lean individuals.

A metanalysis in 2011 showed that obesity may influence outcomes for patients with H1N1 influenza infection. A body mass index (BMI) above 40kg/m² was associated with increased mortality, though not in all studies.¹

A paradox in infectious disease outcomes?

In a recent study of patients hospitalised as a result of different infectious diseases, there seemed to be higher fatality rate in individuals with a lower BMI.² This suggests that having a higher BMI may convey some protective effect, and the question of whether obesity is associated with higher mortality from infectious disease remains open.

Another study that examined H1N1 infection in a group of 400 individuals found no association between obesity and mortality, though people with obesity stayed longer in intensive care and required more mechanical ventilation.

The case of COVID-19

To date, we have learned that adipose tissue expresses very high concentrations of angiotensin-converting enzyme 2 (ACE2) receptors, which are used by the COVID-19 virus to enter the body. The virus could use adipose tissue as a reservoir to replicate and produce cytokine storms. The more adipose tissue a person has, the higher the expression of ACE2 receptors, meaning that the higher the level of an individual’s obesity, the more virus will be retained and replicated.

A study of 257 critically ill patients with COVID-19 found no increase in mortality rates in people with a BMI of 40kg/m² or more.³ Furthermore, people with obesity do not appear to be at greater risk of symptomatic COVID-19. A study of around 4000 patients in New York hospitals in 2020, who needed medical care because of COVID-19 infection, found that around 26% had obesity. This is slightly lower than the prevalence of obesity in the general population.⁴ However, in other cohorts, such as one at Germans Trias Hospital in Badalona, Spain, the proportion of people hospitalised with COVID-19 who had obesity was as high as 40%, with almost an additional 40% with pre-obesity (BMI 27–30).⁵

Obesity, cardiovascular disease and diabetes are among the highest risk factors for hospitalisation from COVID-19. Similarly, the higher the patient’s BMI, the more likely they
Weight regain after bariatric surgery

Rachel Batterham London, UK

Obesity is now widely recognised as a chronic progressive disease. It affects every single organ system in the body and has a marked effect on health, quality of life and life expectancy. Metabolic complications can include cardiovascular disease, type 2 diabetes, fatty liver disease and cancer. Mechanical consequences, such as joint issues and obstructive sleep apnoea, can arise from carrying excess body weight. Depression and anxiety are also prevalent in people with obesity. Furthermore, people living with obesity are at an increased risk of severe and fatal COVID-19.

Maximising weight loss is important, because the prevalence of obesity-related complications increases with body mass index (BMI). Treatment goals are to improve the patient’s health, prevent development of new complications, induce improvement or remission of current complications, and increase life expectancy.

Addressing different complications requires different amounts of weight loss and depends on the patient’s starting BMI. For example, hypertension may improve with a weight loss of up to 5%, whereas addressing cardiovascular disease and type 2 diabetes may need a weight loss of around 15%.

Body weight regulation
Regulation of energy homeostasis is complex. Peripheral signals, reflecting recent nutrient intake and how much energy is stored in adipose tissue, act upon the homeostatic parts of the brain, together with signals from the enteric nervous system and peripheral nervous system. Reward systems and signals regulate the hedonic appetite.

The gastrointestinal tract also plays a critical role in regulating both energy and glucose homeostasis. This is a target for many anti-obesity drugs and for bariatric surgery.

Clinical management of obesity and overweight
The current approach to treatment is based on BMI and the presence of co-morbidities, as shown in the Table on page 13.

All patients, regardless of BMI, will benefit from a healthy lifestyle. Pharmacotherapy is usually considered for people with a BMI of 27 kg/m² or more, who also have co-morbidities. Bariatric surgery may be considered for patients with a BMI ≥ 35 kg/m².

A review of 14 clinical studies found that lifestyle interventions can result in reasonable amounts of weight loss, but most patients eventually regain all the weight they lost. Diets can trigger powerful compensatory mechanisms, such as increased appetite-stimulating hormones, reduced satiety hormones, or reduced energy expenditure. These changes can lead to weight regain.

Bariatric surgery has been shown to lead to more sustained weight loss over long term follow-up, compared with the most effective medical therapy.

How does bariatric surgery work?
In contrast to post-diet observations, patients report a reduction in hunger after bariatric surgery. Increased satiety, changes in taste and smell, and altered food preferences can deter them from energy-dense foods. Functional brain imaging shows a reduction in the homeostatic and hedonic responses to food cues.

Bariatric surgery alters the nutrients and biliary flow through the gastrointestinal tract. This changes a panoply of gut hormones, bile acids and enteric nervous system signalling, which drive improvements in eating behaviour and glucose homeostasis.

Variation in post-surgery profiles
Weight loss and metabolic response to surgery are highly variable. A 2015 study showed that gastric bypass and sleeve gastrectomy resulted in a similar distribution of maximum weight loss, ranging from 5 to 60%.

Most patients reach a nadir in body weight between 12 and 24 months after surgery, and then there is a gradual weight regain. Some do not experience any changes in appetite or food preference. Others may have a good response to surgery initially, but then experience rapid weight regain. This variability matters, because the amount of adipose tissue a person has affects obesity-related complications.
André van Beek

Hypoglycaemia after bariatric surgery

**Table. Current treatment modalities for people with overweight or obesity, based on BMI and co-morbidities.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BMI category (kg/m²)</th>
<th>≥25</th>
<th>≥27</th>
<th>≥30</th>
<th>≥35</th>
<th>≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet, physical activity and behaviour therapy</td>
<td>With co-morbidities</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bariatric surgery</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

Around 70% of variability in post-surgery weight loss is heritable, affected by the patient's circulating levels of appetite-suppressing or -stimulating hormones, such as peptide YY, glucagon-like peptide-1 (GLP1) and ghrelin.

**Predicting weight loss response**

A poor weight loss response can be identified at around 3 months post-surgery. This means there is an opportunity to intervene with other measures and avoid losing the patient to follow-up. It can be disheartening for patients to experience a poor response, so early intervention and support are important.

Studies are underway to try to predict surgical outcomes preoperatively.

**Approaches to inadequate weight loss/weight regain**

We can maximise the health benefits of bariatric surgery by using a polymodal approach, adding lifestyle interventions and pharmacotherapy after surgery. Optimising lifestyle factors should be the first step, followed by a review of any weight gain-promoting medications.

There may be options to revise or enhance surgical therapy. For example, with bypass, it may be possible to extend the limb length, decrease the size of the pouch, or decrease the diameter of the gastrojejunal anastomosis. Converting from one surgery to another, such as converting from a sleeve gastrectomy to a single anastomosis duodeno-ileal bypass, is also quite common.

Bariatric surgery is safe, but revisional surgery carries double the mortality and morbidity of primary surgery, and data to show improved outcomes are lacking.

**Anti-obesity medications**

The availability of anti-obesity drugs varies by region. Naltrexone/bupropion, phentermine and phentermine/topiramate cause an average weight loss of 7% in people prior to bariatric surgery. Studies for every anti-obesity medication show similar efficacy before and after bariatric surgery.

A 2019 study showed that 1.8mg liraglutide caused a significant reduction in glycated haemoglobin and a significant reduction in body weight in patients who still had type 2 diabetes after bariatric surgery. Real world evidence suggests that 3mg liraglutide leads to similar weight loss in those who have had prior surgery and those who have not.

**New pharmacotherapies**

In people with overweight or obesity without type 2 diabetes, the GLP1 receptor agonist semaglutide (2.4mg), injected subcutaneously once per week, resulted in 14.9% weight loss, compared with 2.4% with placebo. Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and GLP1 receptor agonist, which has been shown to help patients with type 2 diabetes and obesity achieve up to 15% weight loss.

With more efficacious pharmacotherapy, we will be able to further improve the health of people with weight regain after bariatric surgery.

In discussion, it was suggested that knowing when to offer surgery to maximise outcomes for people with obesity is challenging, and is likely to change, as new, more efficacious drugs become available. Younger patients may choose to wait for a forthcoming drug that could help them achieve 20% weight loss without surgery. However, this also becomes more challenging, as obesity is a chronic progressive disease.

**REFERENCES**


Hypoglycaemia after bariatric surgery

André van Beek Groningen, The Netherlands

The prevalence of post-bariatric hypoglycaemia is not completely understood. Only a few patients are seen in hospital with hypoglycaemia each year. Around 12% of patients issued with post-surgical questionnaires report moderate to severe complaints, though it is unclear if these would meet the cut-off values for hypoglycaemia. However, investigation with an oral glucose tolerance test (OGTT) or mixed meal test (MMT) tends to show that around 30–80% of patients have hypoglycaemia. Sensors show an even higher prevalence, which means many patients may be unaware that they have hypoglycaemia.

Post-bariatric hypoglycaemia can have a major impact on quality of life. Patients with hypoglycaemia are more likely to experience anxiety and depression after surgery.

**Case study**

A 31-year-old woman underwent gastric bypass surgery 2 years ago. Prior to surgery, she weighed 110kg, with a body mass index (BMI) of 43kg/m² and no co-morbidities. At 1 year after surgery, her weight was 75kg (a BMI of 29kg/m²), which represented a weight loss of 32%. She reported experiencing tremors, perspiration, loss of concentration and hunger over several weeks. These symptoms appeared around an hour after eating and lasted for an hour. They disappeared after eating sweets but recurred quickly afterwards.

This is a classic description of post-bariatric hypoglycaemia.

**Diagnosis of post-bariatric hypoglycaemia**

Diagnosis is confirmed where:

- Whipple’s triad is present
- symptoms occur as a post-prandial event (1–3 hours after eating)
- the patient had prior Roux-en-Y gastric bypass surgery (or other surgery of the upper intestinal tract)
- there are no atypical findings, such as fasting hypoglycaemia or late nocturnal hypoglycaemia.

Testing with OGTT, MMT or glucose sensor analysis is recommended.

The Whipple’s triad includes the presence of symptoms of hypoglycaemia, which
may be autonomic (such as weakness, tremors, perspiration or palpitations) or neuroglycopenic (such as dizziness, drowsiness or confusion). Secondly, these symptoms are found in combination with a low plasma glucose concentration. Finally, the symptoms are relieved when plasma glucose is increased.

There is no absolute cut-off point for plasma glucose, though the lower the level, the more likely a diagnosis will be. A 2021 study suggests glucose below 3.0mmol/l would be consistent with post-bariatric hypoglycaemia. Others have suggested a cut-off of 2.8mmol/L. The Figure (right) shows a very fast glucose resorption in the absence of the native stomach and pyloric function, within around 30min of eating, with hypoglycaemia occurring within 60–120min of eating.

A highly fluctuating glucose concentration throughout the day would also be indicative of post-prandial hypoglycaemia.

**Patients at risk**
Hypoglycaemia is associated with both increased insulin sensitivity and β cell function. Further research has shown that those who undergo revisional gastric bypass surgery are at higher risk of developing hypoglycaemia, perhaps due to vagus nerve damage. Altered bile metabolism following cholecystectomy may also increase risk. Patients with early dumping may also show an increased likelihood.

There are few therapeutic options to address insulin sensitivity, but β cell function can be influenced. In a recent study, blocking the glucagon-like peptide-1 (GLP1) receptor prevented a high insulin response and low glucose nadir, which led to a reduction in symptoms.

**Treating hypoglycaemia**
Post-bariatric hypoglycaemia treatments focus on taming the L cell by reducing the rate of glucose absorption by diet or acarbose, or by decreasing GLP1 and insulin production by use of somatostatin analogues.

Treatment often needs escalation, requiring a combination of diet and medical treatment. A low carbohydrate diet has been shown to be hugely effective. Grade B recommendations include:
- eliminating rapidly absorbable carbohydrates from the diet
- eating six small meals per day
- allowing 30min between eating and drinking
- prioritising high fibre and high protein foods, eaten slowly.

Pharmacological treatment usually begins with acarbose, which slows the rate of glucose absorption. Next, somatostatin analogues may be tried, which are more expensive. These reduce the secretion of GLP1 and insulin. GLP1 analogues have little effect on post-prandial hypoglycaemia, but seem to prompt changes in dietary habits and preferences.

Surgical treatments may include tube feeding into the remnant stomach, which causes almost no glucose fluctuations compared with oral feeding. Banded bypass is no longer recommended. Gastric bypass reversal is an option, shown in a literature review to resolve 80% of cases. Full or partial pancreatectomy should be avoided.

**Future treatment options**
Avecitide is a new GLP1 receptor blocker, which has shown promising results in a study of 18 patients. New research pointing to the role of glucagon in hypoglycaemia could also lead to potential therapeutic targets, such as the closed-loop glucagon system. SGLT-2 inhibitors are another new option.

**REFERENCES**
The forthcoming European Society for Clinical Nutrition and Metabolism (ESPEN) Micronutrient Guideline lists certain micronutrients as at risk of deficiency in patients with obesity, including vitamins B1, B9 and D, and trace elements such as iron, selenium and zinc. The list expands after bariatric surgery. Vitamin B1 deficiency worsens and several fat soluble vitamins, such as A and E, need to be monitored.

Only a few clinical guidelines address these issues. The British Obesity Metabolic Surgery Guideline published in 2020 includes a long list of micronutrients that should be monitored and supplemented in perioperative and postoperative patients. These recommendations do not refer to body composition.

Sarcopenic obesity

A 2018 paper on sarcopenic obesity notes the lack of diagnostic tools for the prevention and treatment of this condition. It concludes that lack of diagnostic tools for the prevention and identification, assessment and treatment of patients with obesity-related muscle loss. As a result, awareness of the relevance of skeletal muscle mass maintenance remains inadequate.

There are different types of sarcopenia. Primary sarcopenia is age-related, while secondary sarcopenia comprises three types:

- activity-related sarcopenia, resulting from inactivity, bed rest, deconditioning or zero-gravity conditions
- disease-related sarcopenia, associated with advanced organ failure, inflammatory disease, malignancy or endocrine disease
- nutrition-related sarcopenia, resulting from inadequate intake of energy and/or protein, as with malabsorption, gastrointestinal disorders or anorexia.

All four types can occur alongside obesity. Sarcopenic obesity affects more than 18 million individuals in Europe, with implications for quality of life and mortality.

Assessing body composition

Sarcopenia can be diagnosed using computerised tomography scans and magnetic resonance imaging. Dual-energy X-ray absorptiometry is a highly accurate and reproducible method of measuring lean mass. Bioelectrical impedance analysis is an inexpensive and rapid alternative, though its accuracy can be impaired by hydration variability.

ESPEN and the European Association for the Study of Obesity recently completed a consensus paper on the diagnosis of sarcopenic obesity. This recommends a three-step procedure consisting of:

- screening based on body mass index, waist circumference and clinical symptoms
- diagnosis based on muscle function and body composition
- staging based on the presence of complications.

A study of body composition after sleeve gastrectomy showed that, while muscle mass as a percentage of body mass remains roughly similar, it decreases in absolute terms following weight reduction. This occurs with any weight loss treatment. In a pilot study, patients who underwent sleeve gastrectomy experienced more catabolism and protein malnutrition than those who were treated with a multidisciplinary intervention programme.

Protein supplementation after bariatric surgery

A 2016 pilot study using commercial protein products to enhance protein intake in patients who had undergone bariatric surgery found that supplementation reduced muscle loss, though not significantly. More recent studies have shown that protein supplementation can improve muscle maintenance, but it takes time.

A more important component is exercise, which can improve outcomes further when added to the nutritional intervention. Resistance exercise has been shown to be slightly more effective than aerobic activity. This could be combined with therapies for ‘pharmaconutrition’, though data are currently limited.

A meta-analysis of 15 interventional trials showed that the combination of nutritional intervention and resistance exercise is currently the best approach.

In conclusion, diagnosis of sarcopenic obesity should be based on body fat mass and decreased muscle function. Therapy comprises a high protein diet combined with an exercise programme that includes resistance training.

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Adipose tissue quality is key to maintaining proper metabolic control. Disruption can lead to major metabolic alterations and resistance to weight loss. When a person gains weight, adipocyte size increases, which results in hypertrophy, stress and hypoxia. This is associated with low grade inflammation which, over time, can lead to accumulation of fibrosis. An increase in adipose tissue also alters adipokine secretion, further impairing the immune response.

Unhealthy expansion of adipose tissue is a dynamic process. Early stages of obesity might involve healthy expansion of adipose tissue, with hyperplasia, hypertrophy and adaptive angiogenesis. However, at a certain point, the vessels are no longer stable, which can cause local hypoxia, adipocyte stress, secretion of inflammatory mediators and fibrosis. Recent research has revealed new insights into adipocyte biology. Previously, the cell cycle was not thought to be particularly involved in the biology of these cells, but new studies show that, in the context of obesity, cell cycle genes can be modified. Knowledge is also emerging around the heterogeneity of macrophage phenotype and function.

**Functional diversity of adipose tissue**

The diversity of cells in adipose tissue is very important. A study in Sweden used spatial single-cell analysis to map the architecture of human adipose tissue, revealing different types of adipocytes, such as perilipin (PLIN), leptin and serum amyloid A cells. These mature adipocytes may influence how adipose tissue responds to insulin.

Progress has also been made in our capacity to isolate precursor cells. For example, we can now perform single-cell RNA sequencing to isolate and characterise different types of progenitors.

**Progenitors in fibrosis accumulation**

There are many progenitor subtypes in different locations and with different fates. Great progress has been made in understanding the fates of these cells. The nature of differentiation by white adipose tissue progenitors can either lead to healthy adipogenesis or to inflammation and fibrosis. In the context of obesity, there are increased numbers of proinflammatory and profibrotic progenitors. Activation of ‘beiging’ could potentially repress adipose tissue fibrosis. How quickly adipose tissue will exhibit unhealthy remodelling (particularly in humans) is not currently known.

**Heterogeneity in collagen distribution**

Examining adipose tissue under a microscope also reveals the heterogeneity of adipose cells. Adipocytes close to fibrotic bands are smaller. There appears to be a relationship between collagen accumulation and adipocyte cell size. Adipocytes engulfed in fibrosis are PLIN-negative, suggesting that fibrosis may be a response to a signal from dysfunctional or dying adipocytes. More research is needed.

**Cellular mechanism of fibrosis**

The cellular actors of fibrosis in adipose tissue include lymphocytes, macrophages, mast cells, endothelial cells, fibroblastic cells and pre-adipocytes. New research on the origin of fibrosis by Marcelin et al. has revealed that myofibroblasts are central to connective tissue remodelling. A mouse model was used to explore the types of cells and signals that contribute to fibrosis. This showed that fibrosis occurs preferentially in epididymal white adipose tissue, with increased expression of different types of collagen. Fibrosis was also associated with increased insulin resistance in obese mice.

Cell sorting showed that stromal platelet-derived growth factor receptor A (PGDFRa+) progenitors are involved in extracellular matrix production. These progenitor cells appear to proliferate and undergo a phenotype switch in individuals with obesity, and may contribute to inflammation in obese adipose tissue. PGDFRa+ cells with high levels of CD9 markers were found to be profibrotic, whereas those with low levels of CD9 were found to be proadipogenic.

At least three major subsets have been found among progenitor cells in white adipose tissue. A 2018 study used single-cell RNA sequencing to identify fibroinflammatory progenitors with high CD9 levels, pre-adipocytes with low CD9 and mesothelial cells with low CD9. Marcelin’s research suggests that these mesothelial cells also contribute to fibrosis in animal models.

**Adipose tissue quality**

Isolating different cell types and characterising different cell subtypes is essential for understanding adipose tissue biology. Recent advances in single-cell transcriptomics have enabled researchers to identify distinct adipose cell populations and understand their functions. However, there is still much to learn about the complex interactions between these cells and their microenvironment.

**Future landscape**

Further research is needed to elucidate the mechanisms driving adipose tissue remodelling and to develop effective therapeutic strategies. New technologies, such as CRISPR-Cas9 editing, offer promising avenues for manipulating adipose tissue metabolism and improving metabolic health.

**Conclusion**

Understanding the biology of adipose tissue is crucial for developing effective treatments for obesity and related metabolic disorders. Continued investment in basic and translational research will be necessary to advance our knowledge and improve patient outcomes.
Translation to human models
Human models confirm the presence of different types of progenitor cells. In human adipose tissue, there is an imbalance between cells with high and low CD9, which is associated with fibrosis, adipose tissue dysfunction and insulin resistance. High CD9 is also associated with high hydroxyproline content in human adipose tissue. There is a positive relationship between the abundance of PGDFRα+ cells with high CD9 and markers of diabetes.

Stiffness of adipose tissue may be associated with fibrosis, though the technology used to measure this involves significant individual variability. Increased stiffness seems to track with increased markers of glucose control. Increased subcutaneous fat mass was associated with less stiff fats.

There is an association between fibrosis accumulation in adipose tissue and aggravation of metabolic complications, such as insulin resistance and markers of non-alcoholic fatty liver disease. In candidates for bariatric surgery, increased accumulation of fibrosis in subcutaneous adipose tissue was associated with less weight loss after 1 year after gastric bypass, as shown in the Figure on page 16. This suggests a link between fibrosis and weight loss variability.

The FAT score
It is possible to measure adipose tissue using a fibrosis score. A fibrosis score of adipose tissue (FAT score) has been developed with stages based on the severity of perilobular fibrosis (PLF) and pericellular fibrosis (PCF):
- stage 0: no PLF or PCF
- stage 1: moderate PLF and/or moderate PCF
- stage 2: severe PLF or severe PCF
- stage 3: severe PLF and severe PCF.

Higher stages have been shown to be associated with a poorer weight loss response to bariatric surgery, independently of other predictors such as age, diabetes, hypertension or fat mass. The FAT score may be useful in predicting those patients who will have a limited response to surgery.

Progenitors and weight loss after surgery
New (unpublished) data show that, in patients with severe obesity and type 2 diabetes, those with more abundant CD9+ high progenitor cells more often saw partial resolution of type 2 diabetes mellitus and a smaller reduction in body fat mass after bariatric surgery than those with lower levels, even where other baseline markers were matched. This suggests that progenitor accumulation could contribute to metabolic impairments and less amelioration of diabetes following surgery.

Therapeutic strategies to limit fibrosis
There is significant variability in how patients respond to dietary, pharmacological and surgical interventions. In future, it may be possible to complement these therapies with treatments that target adipose tissue. Pharmacological interventions are currently being developed, with promising results so far.

Given the differences between phenotypes with stiff fat and loose fat, there is interest in targeting adipose tissue to improve its plasticity.

In the discussion, it was asked if transient elastography (FibroScan) apparatus can be used to scan for adipose tissue. Unfortunately, the same probe cannot be used for liver and adipose tissue.

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The genetics of common obesity in the era of precision medicine
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Both genes and environment contribute to risk of obesity. Environmental changes have become an increasingly important driver of obesity in recent years, but we know from twin and family studies that there is also a strong genetic component. Heritability has been estimated to be between 40 and 70%.

The genetic component of obesity refers to pathways involving multiple proteins and hormones, not just individual genes. More than 80 genome-wide association studies (GWAS) have been performed, identifying at least 1500 genetic loci. The vast majority were first identified in relation to body mass index (BMI). Of note is a new meta-analysis performed by the Genetic Investigation of Anthropometric Traits (GIANT) Consortium. This includes 2.1 million individuals and will soon also include data from the genetic testing company 23andme for a total of 5.6 million individuals. Findings are anticipated in 2022.

Despite these advances, insights have been quite limited. An important understanding is that genes located within specific loci are more often expressed inside the brain than those genes located outside these loci. This suggests that the brain is a strong regulator of energy metabolism in both monogenic and common forms of obesity. This insight was made in 2010 with just 30 GWAS loci. Given the increase in identified loci, it is surprising that more biological components have not been discovered since then. For example, adipose tissue is a known factor in the mechanics of obesity, but rarely emerges in GWAS studies for BMI.

Despite strong genomic associations, it also remains challenging to predict risk and outcomes of obesity. This could be because of the focus on BMI. BMI is a simple outcome that allows analysis of large datasets, but it is a very crude index and, as such, obesity is a heterogeneous condition. BMI tells you nothing about underlying biology, causality, body composition, co-morbidities or age of onset.

How to improve diagnosis of obesity
With more genetic information, it should be possible to identify sub-phenotypes of people with obesity. This will facilitate more precision in prevention, prognosis and treatment.

One method of subtyping is based on adiposity and metabolic consequences, which recognises that not all individuals with obesity have co-morbidities. Another approach is to categorise by subtype based on current risk profile using machine learning. For example, analysis of lipid profiles and other characteristics could develop an overall risk profile. A third approach is to identify subtypes based on potential hedonic causes of obesity, by analysing hunger hormones.

Subtyping by genetic data may be another helpful approach. This would enable subtyping based on underlying pathology and identify variants that uncouple adiposity...
from cardiometabolic co-morbidities. A 2021 study used publicly available GWAS data to compare variants and identify cases where the relationship between two variants was the opposite to what might be expected, such as individuals with a high BMI but low triglycerides.1 Anthropometric traits included BMI, body fat percentage and waist to hip ratio, while cardiometabolic outcomes included high density lipoproteins (HDL) and low density lipoproteins, triglycerides, systolic blood pressure, glucose and insulin. These pairwise analyses resulted in 62 independent loci. For example, the mTOR gene was associated with increased body fat percentage, but with lower risk of type 2 diabetes. While all were identified through this uncoupling strategy, the association signatures were diverse.

Tissue enrichment analysis on these loci showed no evidence that the brain is enriched in these phenotypes, but there is clear evidence that adipose tissue, subcutaneous abdominal fat and other adipose-related tissues and cells are enriched. The variants that connect or disconnect obesity from its cardiometabolic outcomes have a different underlying biology from what is observed when we only look at BMI.

Clusters, variants and risk scores
A cluster analysis identifies three clusters. The first cluster is mainly associated with lipids. The third cluster is associated with type 2 diabetes, glucose levels and blood pressure. The pattern for the second cluster is less clear. A genetic risk score shows a distinct association signature for each cluster.

Individuals can be scored based on variants identified through multi-trait genetics, where BMI is aligned to risk factors. For example, individuals with a high genetic risk score for cluster one are likely to be at higher risk of high adiposity, very low triglycerides and very high HDL cholesterol. Low scores could be interesting, as these might indicate an individual who has a low risk of obesity, but a high risk of certain co-morbidities.

In theory, genetic sub-phenotyping could be applied at birth.

GWAS for body fat percentage
An unpublished GWAS looking at body fat percentage and fat free mass in 554,000 individuals identified nearly 1200 loci across the two categories. Interestingly, the variants associated with an increase in body fat percentage were different from those associated with an increase in fat free mass. Analysis of these characteristics results in six clusters.

Again, these clusters of loci can be used to generate risk scores for different diseases. In young people, some loci, and therefore some aspects of biology, were shown to have an effect in early life while others did not.

This shows that, by using genetics, we can help subtype obesity and identify different parts of the underlying pathology. GWAS of BMI is only one form of gene discovery. More work can be done to think creatively about how we use new data to subtype obesity.

Implications for weight loss interventions
Currently, we take a one-size-fits-all approach to weight loss interventions, based on the assumption that everyone has the same type of obesity. This leads to hugely variable results. Genetic subtyping may help to prescribe the right weight loss intervention for each person.

A recent study classified obesity according to four distinct phenotypes, as shown in Figure 1 below. When different interventions were matched to these phenotypes based on causal mechanisms, weight loss was much more pronounced than when all patients were prescribed the same intervention (Figure 2 below).2

REFERENCES
Pharmacotherapy and multimodal conservative treatment

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Obesity is a complex, progressive and relapsing chronic disease, characterised by excessive adiposity. The focus of obesity management should be on improving patient-centred health outcomes, rather than weight loss alone. An effective way to do this is through conservative multimodal therapy, where various specialists work with the patient to develop an individual treatment plan. This should be based on diet and nutrition therapy, exercise, behavioural therapy and drug treatment, tailored to the individual patient’s needs. People living with obesity face substantial bias and stigma, which contribute to increased morbidity and mortality independent of weight or body mass index. Personal and social stigma can affect the patient’s mental health, which can trigger unhealthy, weight-promoting behaviours. Clinical stigma can be a barrier to systemic preventative approaches and research, and cause treatment inertia.

The weight loss percentage that is needed to ameliorate different co-morbidities varies by condition. Therefore, shifting the focus to health rather than weight status is important. Canada’s new clinical practice guidelines for adults with obesity incorporate this idea.

Obesity management in diabetes treatment

Obesity management is a primary treatment goal for type 2 diabetes, and the two conditions have a similar pathophysiology. Lifestyle intervention is the obvious starting point. The Look Ahead Study of more than 5000 overweight or obese patients with type 2 diabetes showed that an intensive lifestyle intervention was associated with a decrease in body weight and waist circumference, and a nadir in glycated haemoglobin after 1 year. While the results were not sustained over the long term, they remained better than the control group. However, there were also some negative results, including death from cardiovascular causes, myocardial infarction and stroke.

The Diabetes Remission Clinical Trial (DiRECT) found that type 2 diabetes of up to 6 years’ duration can be reversed by weight loss with the help of an evidence-based, structured, weight management programme, delivered in the community by primary care staff. Almost a quarter of patients in the intervention group achieved at least 15kg weight loss at 1 year. Almost half of patients showed remission of type 2 diabetes and were able to cease antidiabetic medication.

The choice of diet strategy affects weight management, cardiovascular complications and mortality. The optimal treatment is a diet that includes about 60% carbohydrate though, in practice, it is the least used approach. Lifestyle interventions are important, but patients are often unable to achieve weight loss through diet alone. The alteration in body weight set point means that weight regain is very common, as shown in the Figure below.3

**Drugs to re-establish body weight set point**

Anti-obesity drug treatments can help modify body weight set point by targeting different neurotransmitters and receptors in the brain. For example, naltrexone–bupropion combination therapy stimulates a pro-opiomelanocortin (POMC) feedback loop, which reduces POMC neuronal activity, thus reducing appetite and increasing energy expenditure. The combination of the two drugs is far more effective than either on its own.

Glucagon-like peptide 1 (GLP1) receptor agonists reduce food intake and body weight by activating complex signalling mechanisms that act on the hypothalamus.4 Liraglutide has been shown to reduce the risk of type 2 diabetes and support weight management over 3 years. It has also been associated with a lower risk of cardiovascular events.

Semaglutide is an emerging therapy which appears to be one of the most powerful weight-loss drugs, though it is not widely available yet. It has been shown to reduce mortality resulting from cardiovascular complications of obesity and type 2 diabetes. A once-daily 2.4mg dose of semaglutide has been shown to reduce body weight by around 15% over 68 weeks, compared with 2.4% in the control group. More than 30% of patients treated with semaglutide reduced their body weight by more than 20%. There were also improvements in body composition, systolic and diastolic blood pressure, and lipid profiles.

Advances are also being seen in GLP1 receptor agonist use in combination with multi-agonist unimolecular peptides such as gastrin, glucose-dependent insulintropic polypeptide (GIP), and others. A trial using a novel dual GIP and GLP1 receptor agonist combination in patients with type 2 diabetes has shown promising effects, resulting in up to 11.3% weight loss. This drug, known as tirzepatide, has been further shown to have very promising effects compared with alternative drugs in a clinical trial.

Another emerging treatment is cagrilintide, which is an amylin analogue that induces leptin sensitisation. This has been shown to have a remarkable effect on weight loss when used in combination with semaglutide.6 These advances suggest a very positive outlook for the treatment of obesity in future.

REFERENCES


Figure. Schematic representation of the natural history of obesity. Reproduced under CC BY-NC-ND 4.0 licence (https://creativecommons.org/licenses/by-nc-nd/4.0) from Eckel et al.“https://doi.org/10.2337/dc11-0447 ©2011 American Diabetes Association and The Endocrine Society."