Eating disorders

Addressing metabolic and endocrine changes

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Eating disorders such as anorexia nervosa are on the increase and the management of affected patients is challenging. Many metabolic and endocrine changes occur with restrictive eating but most resolve once weight has been restored.

Conditions of disordered eating with altered body image, such as anorexia nervosa, are on the increase. Criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed, have facilitated this increase by allowing a diagnosis to be in a wider patient population, including men and younger patients.[1]

The management of patients with eating disorders presents many challenges for GPs. These include addressing the psychiatric illness, often as the practitioner of first contact, and preventing and treating the multiple medical complications that may arise and lead to the highest mortality of any psychiatric illness. To make management even more difficult, not only does starvation lead to physical instability but refeeding (providing the patient with adequate calories and nourishment) itself can cause significant morbidity – known as the refeeding syndrome.

The main metabolic and endocrine changes that occur with the restrictive-type eating disorders are adaptive – that is, they occur to preserve energy for essential body functions and ensure euglycaemia.

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Key points

- **Restrictive eating disorders carry the highest mortality of any psychiatric illness.**
- **Endocrine and metabolic changes in people with these disorders mainly occur to preserve energy and to maintain euglycaemia.**
- **The main goal of treatment is to restore weight.**
- **Low bone mineral density, and resultant increased fracture risk, is one of the long-term complications of eating disorders.**

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These changes mostly resolve once weight has been restored. Long-term endocrine consequences arise mostly through compromised bone health due to starvation, often at times of accrual of peak bone mass in adolescents and young adults.

Refeeding syndrome

Refeeding syndrome is a life-threatening complication of refeeding. It is not a well-defined entity and the reported incidence varies. It is essentially caused by a shift of fluids and electrolytes in malnourished patients who undergo refeeding and the hallmark feature is hypophosphataemia. Depleted phosphate stores due to starvation, an intracellular shift of phosphate with high carbohydrate refeeding and increased requirements of phosphate for cellular processes (such as the synthesis of adenosine triphosphate) can lead to severe hypophosphataemia. Hypophosphataemia, through depleted phosphorylated intermediates, can lead to tissue hypoxia and cardiorespiratory collapse.[2]

Postprandial hypoglycaemia, hypokalaemia and complications of thiamine deficiency are also concerns in this acute phase of refeeding, so close clinical and biochemical monitoring is needed. Fluid retention also often occurs.

Controlled refeeding is the best approach to prevent serious consequences. This involves a slow increase in caloric and carbohydrate intake guided by changes in the clinical situation and by electrolyte imbalance. Specialist dietitian support is ideal but is not always available. Recommended supplementation during refeeding is with thiamine (300 mg daily) and phosphate, potassium, magnesium and zinc titrated to serum levels.[3]

Electrolyte abnormalities

Sodium

Hyponatraemia is a frequent electrolyte abnormality in patients with an eating disorder. The causes of this are varied and a thorough history and examination are important to make a diagnosis and assist in management. Causes of sodium deficiency include:

- psychogenic polydipsia (i.e. excessive intake of water, often used to increase weight before a routine check-up)
- depletion of blood volume (due to dehydration through decreased intake)
- renal salt wasting
- use of medications (i.e. selective serotonin reuptake inhibitors) causing syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Assessment of volume status is inherently difficult but measurement of blood pressure, urine and serum osmolality and urinary sodium levels, and the taking of a medication history can help in finding the cause of hyponatraemia.

Hyponatraemia in this setting is mostly mild (130 to 135 mmol/L) but more severe cases with neurological adverse outcomes have been described.[4] Escalation of management of the patient to an emergency department for consideration of inpatient treatment has to be considered if there is severe hyponatraemia (sodium levels <125 mmol/L) or if the patient is symptomatic. Treatment depends on the underlying cause.

Potassium

Hypokalaemia occurs frequently and mainly in patients with purging behaviour. It is often severe and found together with metabolic alkalosis. Hypokalaemia is a result of potassium depletion but also activation of the renin-aldosterone system in patients with chronic dehydration due to starvation and ongoing purging (Pseudo Bartter syndrome) leading to urinary losses.[5] If it is severe (potassium levels <2.5 mmol/L), admission to hospital for cardiac monitoring is usually necessary.

Acute treatment of hypokalaemia should involve slow rehydration as well as potassium replacement, both orally and intravenously.[5] Once the patient is eukalaemic, treatment of purging behaviour with ongoing potassium replacement is warranted. Hyperaldosteronism can persist for weeks after rehydration, even if purging ceases, and this can promote development of peripheral oedema.

Tissue involvement

Liver function derangement in starvation is common, and transaminase levels can be elevated two to four times above the upper limit of normal due to cell apoptosis, returning to normal with refeeding. However, if transaminase levels increase during refeeding, steatosis can be the cause.[6]

Constipation and bloating are common symptoms experienced during refeeding; delayed gastric emptying and decreased colonic motility may be the underlying causes. Expectant treatment is indicated. Stool softeners can be used but stimulant laxatives should be avoided. A serious complication of starvation can be superior mesenteric artery syndrome, due to compression of the duodenum by the superior mesenteric artery with loss of the mesenteric fat pad in starvation. This causes gastric outlet obstruction and can present in mild cases with postprandial epigastric pain or early satiety and in more severe cases with severe nausea and bilious vomiting, warranting urgent inpatient treatment.

The cardiac complications hypotension and bradycardia generally resolve with refeeding. There may also be a loss of left ventricular muscle mass leading to reduced cardiac output and pericardial effusions.[7,8] Treatment is again expectant and aims to restore weight. QT prolongation due to electrolyte imbalance or medication use should be checked. ECG assessment and monitoring are part of the baseline investigations when assessing a patient with an eating disorder. Postural hypotension or tachycardia often indicate compromised cardiovascular stability.

Skeletal muscle bulk is lost in starvation but recovers when weight is restored.[9] Refeeding helps both muscle bulk recover and improves wellbeing and cognition.

A central fat distribution has been repeatedly noted in the literature when patients with anorexia – both men and women – have been refed.[10] In the long term, such a central fat deposition may increase metabolic risk.

Main endocrine issues

Glucose metabolism

A major management concern in primary practice in patients with eating disorders is hypoglycaemia, although it is often asymptomatic. The difficulty is deciding when recurrent hypoglycaemia warrants specialist or acute care referral or if it can be managed by the GP. Usually patients with a lower body mass index have lower levels of insulin than patients with a healthy body weight, the lower insulin levels allowing counter-regulatory mechanisms such as lipolysis and glycogenolysis to occur to maintain euglycaemia.[11]

Hypoglycaemia can be a sign of severity of anorexia nervosa, reflecting depleted hepatic glycogen stores.[6] Starvation-induced hepatitis is common in patients with severe undernutrition, and impaired gluconeogenesis can be a consequence.[12] The only effective treatment is refeeding and re-establishing hepatic glucose and glycogen stores. If maintenance of normal blood glucose levels is significantly impaired with consequent moderate-to-severe hypoglycaemia (hypoglycaemia requiring assistance from others), urgent referral of the patient for refeeding in a supervised inpatient setting is warranted; continuous nasogastric feeding is often required. Enteral glucose replacement is preferred to intravenous glucose especially in the setting of thiamine deficiency, which occurs frequently in these patients.

Initial refeeding with low-carbohydrate loads is recommended because of postprandial hypoglycaemia as part of the refeeding syndrome. This is caused by insulin surges following high-carbohydrate meals.

Thyroid function

Thyroid function tests are often ordered by GPs to exclude other causes for weight loss in patients with eating disorders. Often the results of these tests suggest nonthyroidal illness ('sick euthyroid') – normal or low thyroid-stimulating hormone levels with low triiodothyronine levels and normal-to-low thyroxine levels. This is an appropriate adaption of the body to starvation and undernutrition in an attempt to preserve energy.[13] Treatment with thyroid hormone replacement is contraindicated and management of such abnormal thyroid function tests is expectant. Thyroid function should normalise with weight restoration, often with an initial increase in thyroid-stimulating hormone levels but normal triiodothyronine and thyroxine levels.

Gonadal function and fertility

Often the most obvious endocrine complication of undernutrition in women can be primary amenorrhoea (i.e. no menarche) or secondary amenorrhoea (i.e. loss of periods for more than three months after initial menarche). Affected patients should be referred for specialist review. Male hypogonadism can cause nonspecific symptoms, especially in adolescents.

As eating disorders are prevalent in adolescence, primary amenorrhoea is a common issue and often leads to investigation of pituitary function. Gonadal steroid testing should be part of screening in men with an eating disorder. Starvation and excessive exercise, which can be a component of an eating disorder, cause hypogonadotropic hypogonadism (low levels of luteinising hormone, follicle-stimulating hormone, estradiol and testosterone) due to a loss of the pulsatility of gonadotropin-releasing hormone (GnRH) release. This GnRH pulsatility is influenced by leptin, a hormone important in adaptation to undernutrition. Leptin levels drop in starvation and GnRH release decreases.[14]

Women with eating disorders present more frequently to fertility clinics than women without eating disorders and are twice as likely to have received treatment or assistance with conception.[15]

It may be appropriate to prescribe hormone replacement therapy in the form of the oral contraceptive pill to women with amenorrhoea due to an eating disorder, even if there is no need for contraception. However, this is not evidence based, especially in terms of bone protection, and may create a false sense of reassurance in the patient. Data regarding testosterone replacement therapy in men with an eating disorder are not available.

Menstruation resumes in most women if they regain and maintain weight closer to their ideal body weight for at least six months. Up to 15% of women remain amenorrhoeic for reasons that are not entirely clear.[16] In women with amenorrhoea there is the possibility that ovulation can occur, so rates of unplanned pregnancies are unexpectedly high in this patient group.[17] Patients who are in a sexual relationship need to be counselled about this possibility and contraception should be discussed as pregnancy can lead to poor outcomes for both mother and fetus.[18]

Bone health

Compromised skeletal integrity is the most common long-term endocrine consequence of a restrictive-type eating disorder that leads to specialist referral. Even with recovery and maintenance of weight, the risk of osteoporosis in patients with an eating disorder remains higher than in those without such a disorder.[19] This is due to a combination of factors, including the following:

- Eating disorders commonly occur at the time of peak bone mass accrual in puberty and early adulthood.
- Low gonadal steroid levels and low muscle mass also contribute to increased risk for osteoporosis.
- Higher than usual cortisol levels, a stress response due to starvation, compromise bone health.
- Growth hormone resistance that occurs with an eating disorder leads to low insulin-like growth factor 1 levels. Insulin-like growth factor 1 is an anabolic bone mediator and growth hormone resistance is an adaptive response to assure euglycaemia by promoting the mobilisation of fat stores and lipolysis.[20,21]

Although patients with eating disorders are often younger, osteoporotic T-scores (<-2.5 standard deviations) translate into increased fracture incidence.[22]

When an eating disorder has been diagnosed and if the illness persists, it is prudent to monitor a patient's bone mineral density

(BMD) and to repeat this assessment yearly. Treatment with calcium supplementation is usually necessary. Vitamin D levels can be normal, especially in patients in whom exercise is a component of their behaviour, but these should be maintained above 50 nmol/L with supplementation if necessary.

Treatment of low bone density in this young cohort is limited. Weight restoration (and consequent resumption of periods) is the treatment with the best evidence for improving BMD. Use of the oral contraceptive pill has not been shown to improve BMD (in a few studies with small patient populations) with up to 19 months of treatment.[23-25] One study in females with anorexia and osteoporosis showed improvement of BMD by 4% with transdermal oestrogen (plus progesterone).[26] There are no studies investigating testosterone replacement therapy for men with anorexia nervosa.

One study of oral bisphosphonates has shown some effect in improving BMD but these drugs are difficult to use in this young cohort due to their teratogenicity.[27] Use of bisphosphonates may be a reasonable option in men with an eating disorder, but such treatment has no evidence base. Teriparatide was used in a study of women with an eating disorder and showed significant improvement in BMD, but again in this young patient cohort effects on the developing fetus are unknown.[28] Denosumab has not been studied in patients with eating disorders but is a potential option as it has a shorter half-life than the bisphosphonates; however, contraception has to be maintained for at least six months after its use.

Conclusion

Eating disorders are relatively common in our population. However, affected patients often go undiagnosed and present with an endocrine problem or are found to have abnormal endocrine tests. The primary treatment for medical consequences of eating disorders is to ensure better energy intake with subsequent weight regain and not to use endocrine replacement therapy. In particular, for those with a restrictive-type eating disorder of some years' duration, there is a substantial decrease in BMD that needs to be monitored closely and may require specialist review to guide targeted treatment.

During any refeeding, close monitoring with frequent blood tests is important as well as preventive supplementation with mainly thiamine and phosphate.

Management of these complex patients is challenging in general practice and is most effective with a multidisciplinary team. Good resources for referral processes and advice in managing patients with an eating disorder can be found on the Centre for Eating Disorders website (www.cedd.org.au). **ET**

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A list of references is included in the online version of this article (www.endocrinologytoday.com.au).

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