Endocrine Function in Eating Disorders Associated with Weight Gain and Weight Loss

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Abstract

The objective of this paper is to give a brief review of the endocrinology of eating disorders leading to excessive weight gain and excessive weight loss in humans. Normal and abnormal hormonal control are discussed and some clinical laboratory tests are cited.
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Introduction

The balance of energy in the body is dependent upon a complex system of pathways that control hunger and satiety as well as rate of energy expenditure. Many hormones are released into the circulation to signify hunger and satiety. These hormones act as signals to the central nervous system, most notably to the hypothalamus, to trigger central neuropeptides to modulate appetite. In people with normal eating habits, this system is tightly regulated to maintain hunger and satiety and energy expenditure; however, in people with eating disorders that lead to excessive weight gain or loss, this system may be altered. A normal balance of energy consumption and energy expenditure is needed to sustain a constant body weight, and signals that trigger hunger and satiety allow the body to do that. Neuronal circuits are responsible for maintaining energy homeostasis, and they regulate hunger and satiety via neuropeptides. An important regulator of energy homeostasis is the arcuate nucleus (ARC). It incorporates two populations of neurons, one that stimulates the intake of food and one that inhibits the intake of food. The neural circuit that stimulates food intake does so by expressing neuropeptide Y (NPY) and agouti-related peptide (AgRP). In addition, the hormone ghrelin is orexigenic and communicates with the hypothalamus to promote increased food intake and decreased energy expenditure. The neural circuit that inhibits food intake does so by expressing the neuropeptides pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART).[1] Other signals that are anorexigenic and thus suppress food intake and increase energy expenditure are leptin, insulin, glucagon, cholecystokinin (CCK), and corticotropin-releasing hormone (CRH). Thyroid hormones also play a role in energy expenditure. In addition, the balance between energy intake and expenditure affects the deposition of energy stores. Energy is stored in white adipose tissue (WAT), which is regulated in part by cortisol and insulin, and brown adipose tissue (BAT), which is regulated by thermogenin.[2]

Hormones Associated with Weight Gain and Weight Loss

Hormones and Obesity:

NPY , a neurotransmitter composed of thirty-six amino acids, is very abundant throughout the brain, and the level of NPY in the hypothalamus is important for long-term energy homeostasis.[3] The level of NPY rises during periods of fasting and falls after a person eats; thus, a rise of NPY levels leads to increased food intake and decreased energy expenditure. The NPY interacts with the ipsilateral paraventricular nucleus (PVN), and the release of NPY in the PVN triggers feeding episodes. It has been demonstrated that when NPY is injected intracerebroventricularly (ICV) into the PVN over a period of time, hyperphagia results. It has also been demonstrated that central administration of NPY causes a decrease of energy expenditure and thus reduced brown adipose tissue (BAT) thermogenesis.[1] Rodent models of obesity have shown that overactivity of the

projection of NPY to the PVN contributes to the hyperphagia and reduced energy expenditure that eventually results in obesity in the rodents. On the contrary, when obesity is induced by the diet rather than overactivity of the ARC-PVN projection, the levels of hypothalamic mRNA decrease and non-NPY receptors in the lateral hypothalamic area (LHA) become up-regulated. It appears that the hyperphagia leading to dietary-induced obesity is not caused by the activity of ARC NPY, suggesting that the decreased levels of NPY observed in dietary- induced obesity may be due to a compensatory mechanism by ARC NPY to try to limit hyperphagia and weight gain.[3]

Ghrelin, a twenty-eight amino acid gastric peptide, is an unusual gut hormone because it stimulates hunger rather than satiety, as the other gut hormones do. It increases appetite and food intake, and its levels are highest during periods of negative energy balance (i.e. fasting) and lowest following a meal. It also stimulates the secretion of growth hormone and, to a lesser extent, enhances the release of insulin. Ghrelin mediates its orexigenic effects via the ARC NPY and AGRP .[4] c-Fos expression within these neurons increases after ghrelin is administered peripherally, while surgical removal of the ARC results in the failure of ghrelin to stimulate food intake.[1] Studies on animals have demonstrated that administration of ghrelin both centrally and peripherally increases caloric intake, and the injection of antibodies to ghrelin prevents feeding brought on by fasting. In addition, one study showed that when ghrelin is given intravenously to humans prior to a meal, there is a 28% increase in the intake of food.[5] In people with eating disorders, the concentration of ghrelin is altered. In patients with binge eating disorder and obesity, the fasting plasma ghrelin level is decreased relative to that seen in patients with anorexia nervosa but equal to or higher than that observed in control subjects, suggesting that there may be a time frame and/or resistance factor involved with ghrelin and these diseases.[6]

In addition, the binge eating obese patients also lack the post-prandial suppression of ghrelin secretion, which may be partly responsible for their eating habits and excessive weight gain. Similarly, morbidly obese patients suffering from Prader-Willi syndrome have significantly increased ghrelin concentrations, which may play a role in the severe hyperphagia seen in these patients.[3]

Another hormone whose levels in the body are altered in obesity is growth hormone (GH), or somatotropin. GH is a 190-amino acid protein hormone that is secreted by somatotroph cells in the anterior pituitary. GH increases the rate of energy expenditure by stimulating the metabolism of protein, carbohydrate, and fat. It causes the anabolism of protein in many tissues, helps maintain normal blood glucose levels, and stimulates adipocytes, or fat cells, to break down triglycerides and inhibits their ability to uptake circulating lipids.[7] Normally, the secretion of GH is highest during periods of fasting and the levels quickly drop post-prandially, following the same pattern as ghrelin. In the obese individual, however, this pattern is not seen because the secretion of GH is greatly diminished.[8] This decrease in growth hormone secretion leads to reduction in the rate of energy expenditure.

Many anorexigenic signals are in place to induce satiety and suppress the appetite. Leptin is a 146-amino acid peptide hormone that is synthesized mostly by adipocytes of white adipose tissue (WAT), although it may also be secreted to a lesser extent by brown adipose tissue (BAT), the placenta, the stomach, breast tissue, and skeletal muscle.[3] The amount of circulating leptin is proportional to the amount of adipose tissue. It acts as a signal to the areas of the brain that regulate feeding behavior by signaling the mass of the adipose tissue, and is therefore an indicator of both food intake and energy stores. In people of normal body weight, a decrease in the level of circulating leptin is a signal of the need for food intake, while an increase of leptin inhibits feeding via inhibition of the NPY/AgRP neurons.[1] In people with hyperphagia and obesity, leptin is over-secreted and the counter-regulatory activity of leptin appears to be lost. It is believed that patients who suffer from hyperphagia and obesity experience leptin resistance, similar to the insulin resistance seen in patients with hyperinsulinemia. This would prevent the patient from receiving the signal by leptin that would inhibit eating, thus contributing to the increased caloric intake.[3]

The first adiposity signal to be characterized was insulin, a major metabolic hormone that is secreted by the pancreas. Insulin is similar to leptin in that the concentration of insulin in the plasma is proportional to changes in adiposity, meaning that the amount of plasma insulin is higher during periods when the energy balance is positive and lower when the energy balance is negative.[1] It provides a mechanism of negative feedback in order to maintain constant body weight and fat mass.[4] However, insulin is different from leptin in that the secretion of insulin increases rapidly post-prandially while leptin concentration is relatively unaffected by short term caloric intake. Once inside the brain, insulin exerts its anorexigenic signal to decrease energy consumption and body weight.[1] Insulin's role in the regulation of food intake has been demonstrated in laboratory mice. When receptors of insulin in the brain are selectively inactivated, hyperphagia and obesity results.[4] In patients with eating disorders and subsequent obesity, insulin levels are elevated and insulin resistance often develops. Insulin resistance prevents the negative feedback mechanism of insulin, leading to further caloric intake and increased body weight.

The first hormone of the gut that was shown to be anorexigenic was cholecystokinin (CCK). It is a hormone that is expressed throughout the gastrointestinal tract, but is mostly found in the duodenum and jejunum.[5] CCK is involved in short-term energy regulation by initiating satiety and meal termination.[9] Following food consumption, intraluminal levels of long-chain fatty acids cause the release of CCK from the gut. CCK exerts its actions by activating the vagal fibers and sending satiety signals to the hypothalamus. It has been demonstrated that intravenous administration of CCK to levels equal to physiological post-prandial concentrations causes the decrease of hunger and lowers the intake of food.[4] Studies have demonstrated that genetic deletion of CCK receptors in the hypothalamus of rats leads to hyperphagia and obesity.[1] Therefore, in patients with eating disorders leading to obesity, it is possible that the CCK receptors are defective, or the secretion of CCK post-prandially is impaired. CCK may also take part in long-term energy regulation by acting synergistically with leptin. When leptin is administered centrally, the action of CCK is enhanced, and the use of CCK with leptin leads to more weight loss during the same time period than with leptin alone.[9] On the other hand, when CCK antibodies and antagonists to CCK receptors are administered to rodents, weight gain results.[1] The overall effect of CCK is to decrease the amount of food intake and increase the rate of energy expenditure.[3]

Another anorexigenic hormone is corticotropin-releasing hormone (CRH). CRH is a 41-amino acid peptide neurohormone that is produced by the hypothalamus and causes the release of corticotropin from the anterior pituitary. CRH has many biological functions, one of which is the regulation of energy homeostasis. CRH is part of the CRH system, a neuronal energy balance circuit that causes a decrease of food intake and an increase of energy expenditure. Studies have demonstrated that obese individuals have reduced amounts of CRH. In obese rats, the infusion of CRH into the brain results in decreased energy gain (reduced weight gain), supporting the theory that obesity in rats is due to decreased levels of CRH. In another experiment, the injection of an inhibitor ($CRH_{(6-33)}$) to the CRH-binding protein (CRH- BP, a protein that can inactivate CRH), results in a reduction of weight gain in obese Zucker rats.[10]

Pancreatic glucagon is believed to be a satiety hormone and has demonstrated the ability to inhibit food intake. Glucagon stimulates the release of glucose from stores in the liver, thus increasing the level of circulating glucose. As with other satiety hormones in eating disorders that lead to weight gain, the ability of glucagon to induce satiety is blunted. The level of glucagon following a meal is dependent upon the type of food consumed: a meal high in protein leads to an increase in the level of glucagon, but a meal high in carbohydrates leads to a decrease in the level of glucagon. The decrease in glucagon after a carbohydrate- rich meal likely leads to a decrease in the satiety signal and thus a higher intake of food.[11]

Additional hormones that are affected during weight gain are the thyroid hormones. A function of the thyroid hormones is the stimulation of energy expenditure. They are very important to the regulation of many metabolic processes. In obese individuals, the concentration of thyroid hormones is decreased, leading to decreased metabolism and energy expenditure.[12]

Excessive weight gain due to eating disorders results from an intake of energy in excess of energy expenditure. Excess energy is stored in adipocytes as triglycerides. Triglycerides are the body's primary form of energy reserve. Lipoprotein lipase (LPL) hydrolyzes triglycerides and regulates their uptake by fat cells. LPL activity and expression is controlled mainly by insulin and cortisol, and it is important for the deposition of triglycerides among different tissues in the body. Insulin promotes the storage of triglycerides by stimulating LPL activity in adipose tissue, increasing the uptake of glucose, inhibiting the breakdown of lipids, and stimulating the differentiation of adipocytes. Cortisol's effect on energy storage actually promotes weight gain and obesity, possibly via a synergistic effect with insulin on the stimulation of LPL in adipose tissue.[13]

The majority of adipose tissue in adults is white adipose tissue (WAT). WAT actually functions as an endocrine organ. Adipocytes secrete many substances, including leptin, resistin, estrogen, and tumor necrosis factor-α. In adults with obesity, the number of adipocytes can be up to four times greater than that of lean adults. Obese individuals can develop the metabolic or insulin resistance syndrome. Some of the features of this syndrome are insulin resistance, hyperinsulinemia, impaired glucose tolerance, impaired insulin-mediated glucose disposal, and dyslipidemia. Another complication of obesity possibly related to the metabolic syndrome is the deposition of triglycerides in nonadipose tissue.[13]

The other form of adipose tissue is brown adipose tissue (BAT). It is where most of the thermogenesis takes place in infants, but there is very little BAT in adults. BAT contains a large concentration of mitochondria with thermogenin, a mitochondrial uncoupling protein that enhances thermogenesis.[14] Studies have suggested that BAT can play a role in the development of obesity. Mice that are bred to demonstrate a deficiency of BAT exhibit hyperphagia and obesity. When new BAT is synthesized, the obesity resolves.[15]

Some diseases that are often associated with obesity include: Type 2 diabetes mellitus with insulin resistance, cardiovascular disease and stroke, hypertension, pulmonary dysfunction, gallstones, and endocrine abnormalities.[13] The obesity may be causal, may aggravate the condition, or may be the result of a common underlying defect. When working up a patient with unexplained obesity, one should include tests for these diseases as part of the differential diagnosis. Timed blood glucose and blood insulin tests will confirm or rule out diabetes mellitus. A lipid profile including total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides will be useful when assessing potential cardiovascular disease and stroke. Renal function and other causes of hypertension can be evaluated with blood and urine levels of creatinine and urea, and blood levels of angiotensin, sodium and potassium, and osmolality. Tests for pulmonary dysfunction should include blood gases and electrolytes. Gallstones and liver disease could require testing for bile acids, bilirubin, and liver enzymes such as aspartate transaminase [AST] and alanine transaminase [ALT]. Among the more common endocrine abnormalities associated with obesity are Type 2 diabetes mellitus (mentioned above), hypothyroidism, and Cushing's syndrome. Thyroid status can be assessed with a total thyroxine (total T_4) test and a thyroid stimulating hormone (TSH) test. Most hypothyroid patients have primary disease and present with an abnormally decreased T_4 and abnormally increased TSH. A few patients will have central hypothyroidism (pituitary or hypothalamic disease) and present with both low T_4 and low TSH. More exotic forms such as the inability to convert T_4 to T_3 do exist but are very rare. Cushing's syndrome can be assessed with blood cortisol levels and these should be timed samples to verify the presence or absence of a circadian rhythm. Tests for adrenocorticotropic hormone (ACTH) and a dexamethazone suppression test will help establish the source of the excess cortisol. Inappropriately low testosterone in an obese male may be a symptom of genetic disease, trauma, or infection and deserves further workup. Abnormally elevated estradiol and inappropriate hormonal rhythm in an obese female may signal a neoplasia and deserves further workup. Tests for hormones such as NPY, ghrelin, and leptin require specialized collection and are currently performed in a research/reference laboratory. They should be ordered only after the more obvious tests have failed to diagnose the problem.[16]

Hormones and Anorexia Nervosa:

Anorexia nervosa is an eating disorder characterized by self-starvation that is manifested by extreme anxiety about body weight and size. It is a serious eating disorder and mental health condition that can have significant health consequences and can become life-threatening. The vast majority of Americans who suffer from anorexia nervosa are girls and women. It typically begins during early to mid-adolescence and is one of the most commonly diagnosed mental health conditions in young American women. Anorexia nervosa also has one of the highest death rates of all mental health illnesses, resulting in the deaths of 5-20% of individuals who suffer from it.[17]

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM) published by the American Psychiatric Association, there are four primary criteria for diagnosis of anorexia nervosa: refusal to maintain at least the minimum body weight considered normal for age and height, extreme fear about gaining weight or becoming "fat" despite being underweight for age and height, having a distorted image about one's body size or being in denial about the possible severe consequences of being underweight, or amenorrhea for three consecutive menstrual cycles in postmenarcheal females. The diagnosis of anorexia nervosa is based on many tests and exams, including a physical exam, psychological evaluation, and laboratory tests.[18]

Physical examination involves several measurements, including checking height and weight. A person with anorexia presents with a body weight about 15% lower than what is expected for the patient's height, age, and physical activity. The vital signs are also checked, which may reveal hypotension, bradycardia, or hypothermia. The patient may also demonstrate mid-systolic click of mitral valve prolapse upon physical examination. In addition, the patient may also present with peripheral edema, thinning hair, lanugo, dry skin, poor skin turgor, or obvious emaciation.[19]

A psychological examination is performed with suspected cases of anorexia nervosa to gain insight into of the patient's thoughts, feelings, and eating habits. [18] Several psychological characteristics can indicate anorexia nervosa. The patient may be preoccupied with her weight, dieting, food, caloric intake, and the number of fat grams she eats. She may make comments about feeling "fat" even after becoming underweight. She may withdraw from family and friends, deny hunger, make excuses to avoid mealtimes or other situations in which food is present, or she may develop food rituals. In addition, she may adopt a very excessive exercise routine that she adheres to even during illness, injury, or fatigue.[17]

No specific laboratory test exists to diagnose anorexia nervosa, but there are a plethora of tests available to indicate anorexia nervosa and determine health status of the patient. A chemistry panel may indicate hyponatremia due to excess water consumption; it may also indicate low serum phosphorus levels. Although liver function tests may be a little elevated, the levels of albumin and protein are usually normal. Leukopenia and thrombocytopenia may be demonstrated with a complete blood count.[19] The endocrinology of a patient with anorexia nervosa may also be altered. This includes the hormones of the hypothalamus and pituitary gland, thyroid hormones, adrenal hormones, and hormones of the ovary in females and testis in males.

Gonadotropin-releasing hormone (GnRH), also known as luteinizing-hormone releasing hormone (LHRH), is a hormone of the hypothalamus that controls sexual development and reproduction. GnRH acts on the anterior pituitary by binding gonadotroph receptors and stimulating the synthesis and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The malnutrition that accompanies anorexia nervosa causes a decline in GnRH activity at the level of the pituitary, which results in a dramatic decrease in the numbers of GnRH receptors on the pituitary gonadotrophs.[2] The reduced secretion of GnRH in anorexia nervosa causes a decline in the secretion of LH and FSH. FSH is responsible for the development of the ovarian follicle in women, and FSH and LH both cause the secretion of estrogen from the follicle. LH is also responsible for ovulation and the production of progesterone from the ovary. FSH and LH are secreted in different amounts during the menstrual cycle. In men, FSH stimulates testicular

growth and aids in spermatogenesis. LH acts on the Leydig cells of the testes to stimulate testosterone production.[20] Anorexia nervosa can disrupt the natural secretion patterns of LH and FSH in women, leading to primary or secondary amenorrhea and decreased levels of estradiol.[21] Decreased circulating estradiol in turn leads to decreased fat deposition. In men, decreased secretion of FSH and LH results in decreased blood levels of testosterone which is associated with decreased male secondary sexual characteristics.[16]

Thyrotropin-releasing hormone (TRH) is released from the hypothalamus and controls thyroid function. It acts on the anterior pituitary to stimulate the release of thyroid-stimulating hormone (TSH). During periods of starvation, such as anorexia nervosa, the blood[2] and cerebrospinal fluid[22] levels of TRH are depressed. This leads to a reduction in TSH.[2] TSH acts at the level of the thyroid to release the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3). The thyroid hormones are important to the metabolism of the cells of the body. The starvation associated with anorexia nervosa results in decreased levels of T_3 and slightly decreased levels of T_4, while the levels of TSH are relatively unchanged [normal to slightly decreased].[23] Two significant features of anorexia nervosa are the increased conversion of T_4 to reverse T_3 with concomitant diminution of the T_4 to T_3 pathway, and the delayed response of the pituitary to endogenous and exogenous TRH infusion.[24] TRH also acts at the level of the pituitary to stimulate the release of prolactin.[2] The hormones of the serotonin pathway and vasoactive intestinal peptide (VIP) also serve to stimulate the release of prolactin. However, the major regulator of prolactin secretion is dopamine, which acts to inhibit its release.[25] Prolactin is the hormone responsible for the initiation of lactation in women. The levels of prolactin have been reported to be low, normal and increased in anorexia nervosa.[2, 25, 26] Decreased circulating prolactin in anorexia nervosa could be the result of decreased TRH secretion. Arguments have been presented that the cause of the increased prolactin in anorexics is increased stress (hypoglycemia), increased exercise, hypothyroidism, or decreased dopamine due to generalized hypothalamic failure.[24, 25] The increased levels of prolactin perpetuate the hypogonadism seen in anorexia by inhibiting GnRH pulsatile secretion.[26]

Corticotropin-releasing hormone (CRH) is a hormone of the hypothalamus that responds to internal and external environmental stresses. It also acts on the anterior pituitary to stimulate the release of adrenocorticotropic hormone (ACTH) from corticotroph cells. ACTH is responsible for stimulating cortisol secretion from the adrenal glands. Cortisol, a glucocorticoid, causes the release of glucose for use in response to stress. In patients with anorexia nervosa, CRH and cortisol levels are both increased.[27] However, the levels of ACTH do not change. The response of ACTH to CRH is actually repressed.[28] The increase in CRH depresses the reproductive aspects of the patient. CRH hinders the release of GnRH, and cortisol and other glucocorticoids inhibit the release of GnRH at the level of the hypothalamus, the release of LH at the level of the pituitary, and the release of estrogen and progesterone at the level of the ovaries and testosterone at the level of the testes.[27]

Growth hormone releasing hormone (GHRH) is a hormone of the hypothalamus that stimulates the release of growth hormone (GH) from somatotroph cells in the anterior pituitary. GH plays a major role in several physiological processes, most notably growth and metabolism. Its chief role is to induce the secretion of IGF-I from the liver and other tissues, which then acts on chondrocytes to stimulate bone growth.[7] In patients with anorexia nervosa, the secretion of GH is increased, although the secretion of IGF-I is decreased. GH also has an increased response to GHRH.[28]

The hormone responsible for maintaining normal plasma osmolality is antidiuretic hormone (ADH), also known as vasopressin. It is secreted by the posterior pituitary and stimulates the reabsorption of water at the level of the kidney. Anorexia nervosa can cause inappropriate secretion of ADH, resulting in hyponatremia.[29]

The serum concentration of leptin in anorexia nervosa patients is abnormally decreased reflecting the low weight and low body fat content of these women. Following alimentary supplementation, blood leptin levels increase and this leads to a subsequent increase in

gonadotropins, demonstrating the tie between leptin and the reproductive hormones.[24]

Anorexia nervosa is a serious and sometimes life-threatening disease. It is, however, not the only cause of weight loss. Diseases often associated with extreme weight loss include: Type 1 diabetes mellitus, alcoholism, inflammatory bowel disease, starvation, cancer, renal disease, tuberculosis and/or pneumonia, and parasitic diseases. Such illnesses may be part of the differential diagnosis in someone with anorexia nervosa, and must be ruled out to establish a definitive diagnosis. One of the characteristics of a person with Type 1 diabetes mellitus is weight loss. Diabetes mellitus can be ruled out with the oral glucose tolerance test. If a patient has diabetes mellitus, the oral glucose tolerance test would reveal hyperglycemia, but an anorexia nervosa patient would demonstrate hypoglycemia (low blood glucose levels) due to dietary restriction.[30, 31] One laboratory test that can be used to indicate alcoholism is acetaldehyde-modified hemoglobin (HAA). When alcohol is metabolized, it forms acetaldehyde that can irreversibly bind hemoglobin, called HHA. In patients with alcoholism, HAA is increased. Because the HAA test has such high specificity and sensitivity for alcoholism, HAA levels are not likely to be increased in an anorexia nervosa patient.[32] Inflammatory bowel disease (IBD) may be suspected in cases of weight loss. The detection of certain antibodies can help a physician rule out IBD. Perinuclear anti- neutrophilic cytoplasmic antibody (pANCA) and anti-*Saccharomyces cerevisiae* antibody (ASCA) are autoantibodies that have a sensitivity for IBD of around 71% when used together, and help rule out IBD in patients with non-specific symptoms.[33] A patient with anorexia nervosa would not demonstrate these autoantibodies. While anorexia nervosa is self-starvation, it may be possible to distinguish between voluntary and involuntary starvation by examining a stool specimen for the presence of excess fat, which could indicate starvation due to malabsorption. The fecal fat test allows one to quantitate the degree of steatorrhea. In an anorexia nervosa patient, fat would likely not be present in the stool. Similarly, the fecal occult blood test could demonstrate the presence of a bleeding ulcer with resultant malabsorption.[16] One test that can be used to rule out cancer is a test for calcium levels. In ten to twenty percent of cancers, patients experience hypercalcemia.[34] In contrast, the patient with anorexia nervosa would likely demonstrate a deficiency in calcium. In addition, imaging for tumors and tests for tumor markers can help rule out cancer if such tests are negative, which should be the case for a patient with anorexia nervosa. A urinalysis could be done to help rule out renal failure. A patient with renal failure may demonstrate granular or tubular casts in his urine, while an anorexia nervosa patient would not likely present with such casts. Additionally, a creatinine clearance test and a serum blood urea nitrogen should prove informative. A chest x-ray and microbiological tests for organisms such as *Mycobacterium tuberculosis* and *Streptococcus pneumoniae* will confirm or rule out tuberculosis and pneumonia. Following a confirmed diagnosis of anorexia nervosa, laboratory tests to assess the general health status of the patient should be performed. Included in the general chemistry profile should be an assessment of the calcium status of the patient since many of these patients present with bone loss and psychiatric effects of low calcium.[16, 24]

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