Chapter 10
Secondary Causes of Adipose Tissue Weight Gain

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Pearls of Wisdom

- There is a strong relationship between total energy expenditure, resting energy expenditure, and fat-free mass. The differences in fat-free mass account for a large percentage of total energy expenditure variance among individuals.
- Hypothalamic obesity is rare in humans and is usually due to injury, surgery, tumor, or infiltrative disease.
- Patients with hypothyroidism may have a modest increase in weight due to slowing of metabolic activity, and marked weight gain is uncommon. Conversely, severe obesity may be accompanied by subclinical biochemical hypothyroidism, manifested by mild thyroid-stimulating hormone elevation that corrects with weight loss.
- An increased body mass index in the second and third decades in life, but not later, is more frequently associated with oligo/amenorrhea and polycystic ovarian syndrome in women.
- Obesity, diabetes, and depression often coexist. When assessing causes of weight gain, it is important to review the patient's medication list, as a number of commonly prescribed drugs can cause weight gain, including oral diabetes agents, insulin, steroid hormones (including progesterone), antidepressants, and other mood-altering drugs.

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10.1 Introduction

An increase in excess body weight stems from multiple factors, including socioeconomic and environmental triggers that contribute to an unhealthy lifestyle of increased consumption of calorie-dense foods and decreased work-related and free-time activity**.** However, it is also apparent that there is a strong genetic component in the development of obesity. Genetic factors have been reported to explain a large component of body mass index (BMI) variability in family studies, including twin studies (50–90% of BMI variance), adoption studies (20–60% of BMI variance), and parent–offspring and sibling correlations (20–80% of BMI variance). Wardle and colleagues carried out twin analyses of BMI and waist circumference (WC) in 5092 twin pairs aged 8–11. Quantitative genetic model-fitting confirmed 77% heritability for both BMI and WC. Bivariate genetic analyses showed that, although the genetic influence on WC was 60% common to BMI, there was also a significant independent genetic effect. A very modest shared-environment effect was present for both BMI and WC, and the remaining environmental variance was unshared. Longitudinal studies have identified both parental obesity and childhood obesity as strong predictors of obesity in adulthood. The influence of having one parent with obesity throughout an individual's childhood and adolescence increases that person's risk of obesity in adulthood by 2.2–3.2-fold, with a substantially higher risk if both parents have obesity. In addition, a child who develops obesity at the age of 10–14 years of age has a 22-fold increased risk of obesity in adulthood.

Genome-wide association studies have provided new insights into the genetic factors that contribute to the development of obesity. While the connection between a particular single nucleotide polymorphism (SNP) and adiposity is not always clear, an increasing number of mutated genes can be traced to obesity phenotypes. Leptin deficiency is characterized by hyperphagia and severe obesity, and mutations in the leptin pathway and receptor gene may account for 3–4% of severe, early-onset obesity. Mutations in pro-opiomelanocortin have been described, characterized by a lack of central appetite signaling and hyperphagia. Affected individuals may have hypoglycemia, hypogonadotropic hypogonadism, and adrenal insufficiency. The melanocortin-3 and melanocortin-4 receptors are key in feeding behaviors and mutations of these receptors are found in up to 3% of severe, early-onset obesity in children. Polymorphisms of the "fat mass and obesity-associated" (FTO) gene are associated with adiposity and have been associated with weight regain after lifestyle intervention in children and adults with and without type 2 diabetes mellitus (T2DM). Obesity risk alleles were characterized in 3899 adults with T2DM and overweight or obesity who lost 3% or more of the entry weight after one year, from the Look AHEAD (Action for Health in Diabetes) study, a randomized trial to assess the effects of intensive lifestyle intervention and diabetes support and education. Although SNPs were not associated with weight loss, the FTO gene predicted weight regain in the diabetes support and education group, suggesting variations in the FTO gene may be important in weight regain.

The genetic influence on excess adiposity may occur in two ways. First, genes may serve as the primary factors in the development of obesity. Second, environmental factors may interact upon susceptibility genes that play a role in weight gain. There are major variations in the susceptibility to weight gain among individuals under similar external influences (decreased physical activity and increased calorie intake), depending on the genetic background. Metabolic risk factors for weight gain are reported to include low metabolic rate, increased carbohydrate oxidation, insulin resistance, and low sympathetic activity. Low energy expenditure is one factor that may promote weight gain. Approximately 70% of total energy expenditure (TEE) is utilized for the metabolic basal or resting energy expenditure (REE) needs. These include the REE involved in maintaining body temperature, cellular integrity and ion gradients, cardiac and respiratory muscle function, gastrointestinal motility and secretion, and storage and mobilization of metabolic fuels. Another 10% of TEE is dissipated through the thermic effects of food digestion, and the remaining energy expenditure is from activities of daily living and exercise. There is a strong relationship between TEE, REE, and fat-free mass (FFM), and differences in FFM account for a large percentage of TEE variance among individuals. Piaggi and colleagues studied energy metabolism in 612 healthy adult men and women (mean values for age 29.5 years, BMI 33.0 kg/m^2, and percent body fat 30.9%) with follow-up of 292 subjects after a mean 6.7 years. TEE and REE were measured by indirect calorimetry in a 24-h respiratory chamber, and body composition was assessed by either underwater weighing or dual-energy X-ray absorptiometry (DEXA). The 24-h TEE was inversely related to the rate of weight change ($p = 0.007$) and change in FFM ($p = 0.012$), such that 100 kcal below the expected 24-h TEE corresponded to 0.2 kg/year weight gain, of which 0.1 kg/year was fat mass. Thus, measures of REE and substrate oxidation were predictors of long-term weight change, indicating a small but potentially significant role for a reduced REE in weight gain over an individual's lifetime.

Significant weight loss and loss of FFM may slow the REE. Thus, an important goal during weight loss is to maximize the loss of fat while preserving metabolically active FFM. Johannsen and colleagues studied whether restriction of caloric intake and vigorous physical activity would preserve FFM and maintain REE during weight loss in 16 patients with severe obesity (BMI 49.4 ± 9.4 kg/m^2 and body fat 49 ± 5%). There were measurements of body composition by DEXA, REE by indirect calorimetry, and TEE by double-labeled water. Subjects lost greater than one-third (38 + 9%) of their body weight at 30 weeks, to include 17% from FFM and 83% from fat. Although energy expenditure from physical activity increased significantly, the REE declined out of proportion to the decrease in body mass, demonstrating a substantial metabolic adaptation, with a decline of 504 ± 171 kcal/day ($p < 0.01$). Physical activity did not prevent a significant decline in REE during rapid weight loss, suggesting that patients may be predisposed to weight regain if physical activity and/or caloric restriction are not maintained. The Health, Aging, and Body Composition Study followed body composition change in 147 adults (54% women, 38% African–American) over a weight-cycling period (defined as ≥3% weight loss with weight regain within ±3% of baseline over 2 years) compared to gender- and

race-matched weight-stable subjects. More lean mass was lost during the weight-loss period than was gained during the weight-regain period, especially in men, although not statistically significant when compared to the weight-stable group.

With this background of the genetic influence on body adiposity, and the importance of TEE variability during weight change, this chapter will review the potential endocrine causes of excess body fat, and the role of medications in promoting weight gain.

10.2 Endocrine Causes of Weight Gain

10.2.1 Hypothalamus–Pituitary–Adrenal (HPA) Axis

Hypothalamic obesity is a rare syndrome in humans. In animals, injury to the ventromedial or paraventricular region of the hypothalamus regularly results in obesity. These brain regions are responsible for sensing hunger and satiety, and hyperphagia occurs when the hypothalamus is damaged. Causes of hypothalamic obesity are listed in Table 10.1. Craniopharyngiomas are the most common intracranial tumors of nonglial origin in the pediatric population, and hypothalamic involvement is a major risk factor for obesity in these children. In 90 children with a diagnosis of craniopharyngioma, early reductions in growth rates and late increases in BMI standard deviation (SD) scores were seen. In 48 children with hypothalamic involvement, BMI SD scores were higher at diagnosis and annual follow-up ($p < 0.001$ for both) compared to 42 patients without hypothalamic involvement (Fig. 10.1). Both hypothalamic tumor involvement and BMI SD scores had relevant and independent

Table 10.1 Etiologies of hypothalamic obesity

Single gene mutations	Leptin, leptin receptor, CART, POMC, prohormone convertase-1, MC4R, BDNF (TrkB), single-minded 1(SIM-1)
Genetic syndromes	Prader–Willi syndrome, Bardet–Biedl syndrome
Tumors	Craniopharyngioma, angiosarcoma, cholesteatoma, chordoma, colloid cysts, endothelioma, ependymoma, epidermoid, epithelioma, ganglioneuroma, germinoma, glioma, hamartoma, Langerhans cell, leukemia, meningioma, pituitary macroadenoma, pinealoma, teratoma, metastases
Inflammatory or infiltrative disease	Sarcoidosis, tuberculosis, arachnoiditis, histiocytosis X, encephalitis
Injury	Head trauma, neurosurgery, radiotherapy, aneurysm
Medications	Antidepressants, mood stabilizers, antipsychotics

Adapted from Bereket A, Kiess W, Lustig RH, et al. Hypothalamic obesity in children. Obes Rev. 2012;13:780–98; used with permission

BDNF (TrkB) brain-derived neurotrophic factor (tyrosine kinase B), *CART* cocaine- and amphetamine-related transcript, *MC4R* melanocortin 4 receptor, *POMC* pro-opiomelanocortin

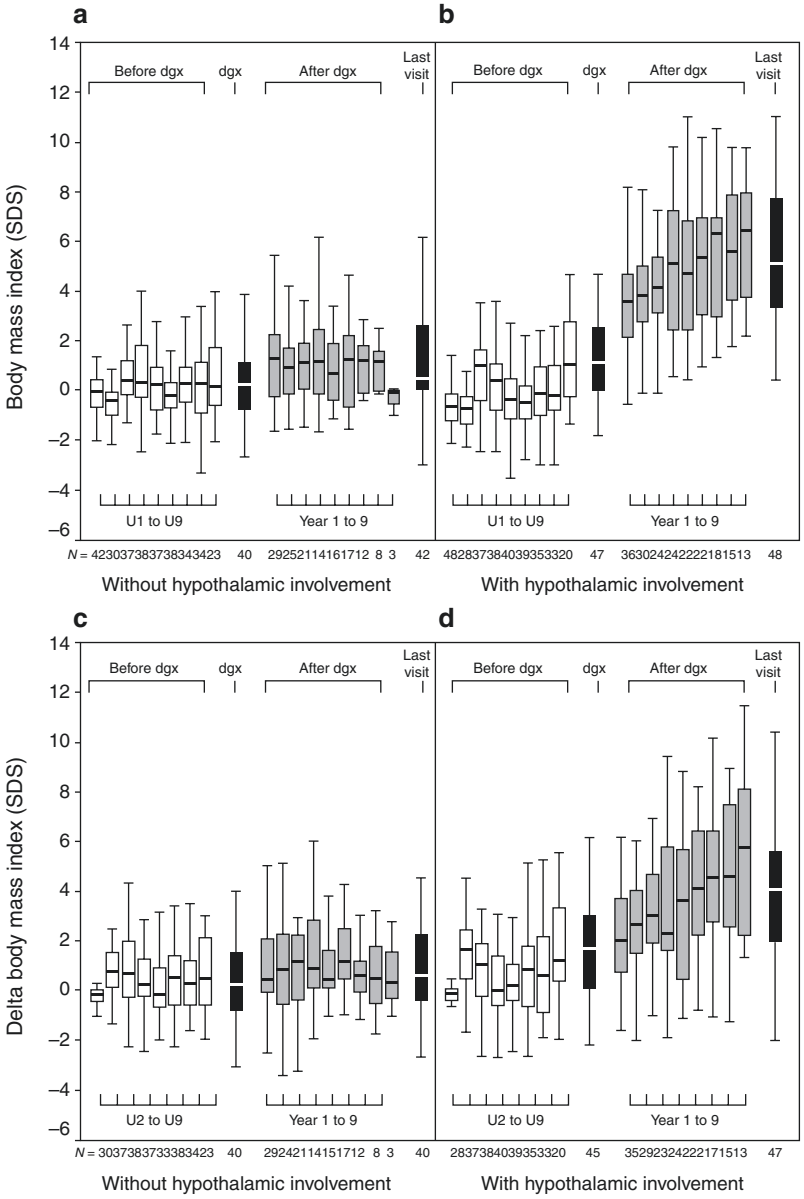


Fig. 10.1 Body mass index (expressed as standard deviation scores, SDS) before, at (mean age 8 years), and after diagnosis of craniopharyngioma and hypothalamic involvement to last visit (n = 90, 50 girls and 40 boys). Ages: U1, birth; U2, third to tenth day of life; U3, third to fourth week; U4, third to fourth month; U5, sixth to seventh month; U6, 10th to 12th month; U7, 21st to 24th month; U8, years 3.5 to 4; and U9, year 5. Data were retrospectively analyzed based on medical records, and results are shown as box plots for patients who presented without (**a**, **c**) or with (**b**, **d**) hypothalamic involvement by craniopharyngioma. (Adapted from Müller et al. 2004; used with permission)

impacts on the development of childhood obesity ($p < 0.001$ for both). In a report of 42 adults treated with surgery and/or radiotherapy for hypothalamic tumors, 52% had obesity at 5-year follow-up compared to 24% at baseline.

Growth hormone (GH) is known to increase lean body mass and reduce fat mass. Long-term GH treatment provides beneficial weight change for children who have either underweight or obesity, independent of the indication for GH therapy. However, GH replacement has also been associated with variable changes in adiposity in children. Changes in BMI SD scores between starting GH treatment and attaining near-adult height were analyzed in 2643 children with idiopathic GH deficiency, 281 children small for gestational age, 142 children with Prader–Willi syndrome, and 1661 girls with Turner syndrome identified from an international growth database. Children with obesity had decreased BMI SD scores, while children with underweight had increased BMI SD scores following GH therapy. Of interest, normal-weight children had an unexpected increase in BMI SD scores during GH treatment. Adult GH deficiency is associated with an increase in abdominal and visceral fat and a decrease in lean body mass. GH replacement in adults has been shown to have significant favorable effects on body composition compared to controls, to include increased FFM and decreased fat mass.

There is dysregulation of cortisol in the setting of excess adiposity. Obesity is associated with changes in adrenal function, which include an increase in adrenal medullary catecholamine output, changes in adipose tissue glucocorticoid (GC) metabolism, and enhanced adipocyte mineralocorticoid receptor activity. It is unknown whether these changes are in part responsible for the increase in adiposity and related metabolic dysfunction, or an adaptive response to obesity instead. GC secretion not only depends on the HPA circadian rhythm but also the intracellular regulation of cortisol by 11-beta-hydroxysteroid dehydrogenase (11ß-HSD). The enzyme 11ß-HSD-1 catalyzes the conversion of the inactive cortisone to active cortisol and thus amplifies GC tissue action in the liver, muscle, and fat. Excess adipose tissue 11ß-HSD-1 activity may be an important component of increased GC receptor activation. In contrast, 11ß-HSD-2 inactivates cortisol into inactive cortisone metabolites, thereby reducing the activation of the GC receptor. This balance of local cortisol activation and inactivation may play an essential role in metabolic disorders that are related to obesity. In addition, cortisol-binding globulin concentrations are often significantly reduced in obesity, resulting in higher free levels of cortisol. Patients with obesity and dysmetabolic syndrome have reportedly higher visceral adipose tissue expression of 11ß-HSD-1, higher adipose tissue expression of the GC receptor, and increased HPA axis activity compared to patients with obesity but without dysmetabolic syndrome. Of interest, weight loss after bariatric surgery has been shown to result in decreased levels of circulating cortisol and lower adipose tissue 11ß-HSD-1 expression, when compared to control subjects with normal weight.

Physiologic stressors can stimulate the HPA axis, which in turn can activate the mesolimbic dopaminergic system, a brain network strongly related to reward. Individuals with a high BMI show a stronger association between chronic stress and weight gain than those with a low BMI who experience similar degrees of stress. Several studies have examined the association of high-fat, high-sugar meal plans

and activity of the HPA axis. Consistent with this notion, stress-related eating is significantly associated with obesity in women. Restrained eating refers to the voluntary cognitive effort to restrict food intake typically for the purpose of controlled weight loss or weight maintenance. High cognitive restraint is associated with increased cortisol concentrations. In addition, both epidemiological and experimental data support the association between sleep deprivation and disrupted physiological rhythms as being a possible risk for developing obesity. It is estimated that approximately one-third of adults in the United States sleep less than 6 h per night. Although studies suggest that restricting sleep may lead to weight gain via increased food consumption, methodologies have been inconsistent and the data, to include effects on energy expenditure, are mixed.

Approximately 5–20% of adrenal incidentalomas present with subclinical cortisol hypersecretion. This disorder has been described as subclinical Cushing's syndrome (CS), characterized by the absence of a clinical Cushing's phenotype and subtle alterations of the HPA axis due to adrenal autonomy, although there is lack of consensus as to the biochemical diagnostic criteria. Zografos and colleagues reported on 21 studies of adrenal incidentalomas and reported an increased prevalence of obesity ($n = 11$ studies, prevalence 25–78%), impaired glucose tolerance or T2DM ($n = 11$, 25–69%), T2DM only ($n = 7$, 16–33%), arterial hypertension ($n = 18$, 45–100%), and dyslipidemia ($n = 7$, 9–71%) irrespectively of adrenal function but being possibly higher in patients with subclinical CS. Rossi and colleagues prospectively studied the clinical and hormonal features of 50 consecutive patients with incidentally discovered adrenal adenomas. All subjects had hormone assays at regular intervals to assess the function of the HPA axis for a median period of 38 months, with comparison to 107 age- and gender-matched controls. For all patients with incidentalomas, T2DM was present in 24%, dyslipidemia in 28%, and BMI >25 kg/m^2 in 36% with significantly higher serum cortisol ($p < 0.001$), lower adrenocorticotropic hormone (ACTH) concentrations ($p < 0.05$), and impaired dexamethasone cortisol suppression ($p < 0.001$). Criteria for subclinical CS were met by 12 (24%) patients, with a BMI >25 kg/m^2 in 50%, T2DM in 42%, and dyslipidemia in 50%. It is noteworthy that obesity, hypertension, T2DM, and dyslipidemia are not specific to cortisol excess and are highly prevalent in the general population. This is especially so beyond the sixth decade of life, when adrenal incidentalomas are more frequent. Nevertheless, improvement in T2DM and insulin sensitivity has been reported after adrenalectomy in patients with adrenal incidentalomas, with or without subclinical CS. Rossi et al. documented that adrenal hormonal features improved in all patients undergoing adrenalectomy but appeared unchanged in patients not treated by surgery during a follow-up period ranging from 9 to 73 months. These findings suggest that subclinical hypercortisolism may contribute to increased adiposity, adiposopathy, and metabolic abnormalities.

The first evidence that cortisol levels were related to obesity and metabolic disease was derived from clinical observations of CS with associated central body obesity, glucose intolerance, and hypertension. The effect of GCs in CS can be explained by the induction of 11ß-HSD-1 and enhanced lipogenic capacity in visceral adipose tissue. GCs increase de novo lipid production in hepatocytes through

increased expression of fatty acid synthase. GCs also promote conversion of preadipocytes to mature adipocytes and have an acute antilipolytic effect on adipocytes. However, the long-term effects of GCs on adipose tissue lipolysis remain unknown, and there is controversy as to whether these mechanisms contribute to fat hypertrophy in adiposopathy.

CS due to bilateral adrenocortical hyperplasia can be classified as ACTH-independent macronodular adrenocortical disease (>1 cm) that is more frequent in older adults, and micronodular disease (<1 cm), more frequent in children and young adults. The cyclic adenosine monophosphate (cAMP) signaling pathway plays a role in bilateral adrenal hyperplasia, either directly due to genetic defects of a central pathway molecule or indirectly via upregulation of ectopically expressed G-protein-coupled receptors in the adrenal cortex. Increased levels of cAMP-dependent protein kinase A (PKA) activity and/or cAMP are increased in adrenocortical lesions, and PKA is known to play an important role in fat metabolism and energy balance. Micronodular adrenal hyperplasia includes a pigmented variant, primary pigmented nodular adrenocortical disease (PPNAD). Mutations of the PRKAR1A gene that codes for the regulatory subunit 1α of PKA (RIα) cause PPNAD. London and colleagues studied CS and non-CS subtypes, both with and without PRKAR1A mutations. PRKAR1A mutations affected cAMP signaling in adipose tissue and were associated with significantly reduced CS-related obesity. BMI and BMI Z-scores were lower in adults with PPNAD and PRKAR1A mutations and in pediatric patients with PPNAD with or without PRKAR1A mutations. PKA activity in adipose tissue differed between CS groups, with higher cAMP levels in patients with PPNAD. Thus, increased cAMP and PKA activity may contribute to increased adiposity and phenotypic differences among CS subtypes.

10.2.2 Thyroid

Many of the actions of thyroid hormone in metabolic regulation involve modulation of other metabolic signaling pathways. Thyroid hormone regulates basal metabolic rate through known targets such as sodium–potassium ATPase, although the overall mechanism is not well established. Thyroid hormone interacts closely with the adrenergic nervous system to generate heat in response to cold exposure, termed adaptive thermogenesis. This process stimulates mitochondrial biogenesis and upregulation of fatty acid oxidation. The conversion of thyroxine (T4) to triiodothyronine (T3), along with the expression of uncoupling protein-1 (UCP1), is required for adaptive thermogenesis in brown adipose tissue, and is stimulated by catecholamines. The UCP1 promoter and the promoter for a rate-limiting enzyme in gluconeogenesis, phosphoenolpyruvate carboxykinase, have a cAMP response element and a thyroid response element in close proximity, and both response elements are required to stimulate gene expression. Thyroid hormone stimulates both lipolysis and lipogenesis and is involved in fatty acid oxidation to mobilize stored triglycerides and generate ATP to meet cellular demands. Regulation of fatty acid oxidation

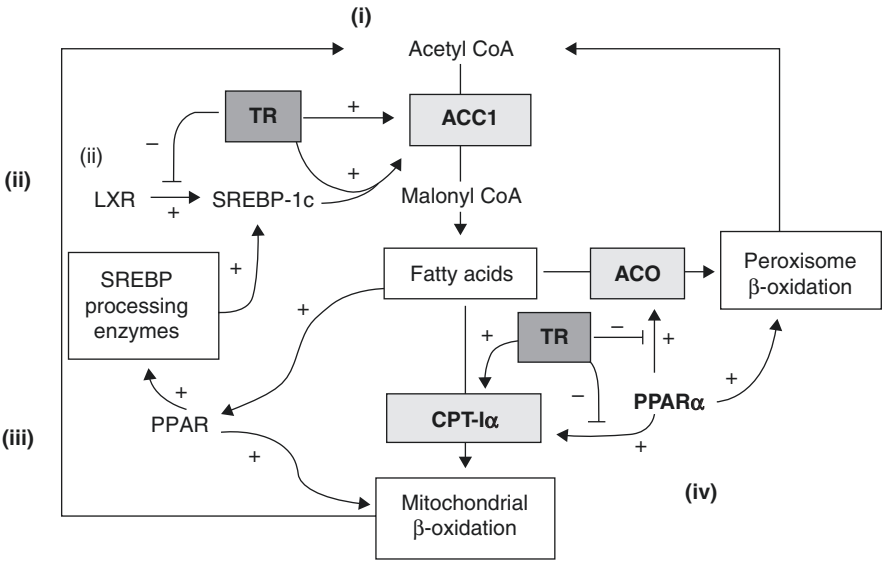


Fig. 10.2 Crosstalk between thyroid hormone signaling and metabolic pathways in fatty acid synthesis and ß-oxidation. (i) Free fatty acid (FAA) synthesis is controlled by acetyl-CoA carboxylase (ACC). Thyroid hormone receptor response element (TR) and sterol regulating element-binding protein (SREBP). (ii) Liver X receptor (LXR) stimulates FFA synthesis by enhancing SREBP-1c gene expression. In the absence of T3, TR competes with LXR. (iii) Peroxisome proliferator-activated receptor (PPAR), an agonist, increases FFA synthesis by enhancing SREBP processing enzymes. (iv) T3 increases FFA oxidation by upregulating palmitoyltransferase (CPT)-Ia. PPARa also stimulates CPT-Ia and acyl–CoA oxidase (ACO), a rate-limiting enzyme. Unliganded TR can block CPT1a and ACO stimulation by PPARa. (Adapted from Liu and Brent 2010; used with permission)

is mainly through key rate-limiting enzymes such as carnitine palmitoyltransferase Iα and acyl-CoA oxidase (Fig. 10.2).

Patients with hypothyroidism may gain weight due to slowing of metabolic activity. Some of this weight gain is fat, but the weight gain is usually modest, and marked weight gain is uncommon. Serum thyroid-stimulating hormone (TSH) levels that are increasing in the normal range or slightly above normal have been associated with a modest increase in body weight. Moreover, there is an inverse correlation between free thyroxine values and BMI, even when free thyroxine levels remain in the normal range. A retrospective analysis of 703 multiethnic children and adolescents found a positive association between TSH concentrations and BMI Z-scores. After adjustment for ethnicity, gender, pubertal stage, and BMI, significant associations remained between TSH levels and hyperglycemia (e.g., impaired fasting glucose and impaired glucose tolerance), and dyslipidemia (e.g., elevated levels of triglycerides, total cholesterol, and LDL-cholesterol). In adults, subclinical hypothyroidism (mean TSH: 6.7 mIU/L) is associated with a slightly higher baseline weight (0.51 kg higher baseline weight per 1 mIU/L higher TSH) in women older than 65 years of age, compared to euthyroid individuals (i.e., TSH 2.2 mIU/L).

However, there is no association observed in men and no weight change over time in women. In contrast, a cross-sectional study in 2037 middle-aged Japanese adults found significant positive associations between the serum TSH and BMI in men only. In a study of 4235 patients with T2DM, patients were divided into two groups based on the thyroid status, those with clinical hypothyroidism on thyroid hormone replacement compared to persons without known thyroid disease. BMI was strongly associated with patients who were found to have hypothyroidism (BMI 32.2 ± 7.4 vs. 29.4 ± 5.7 kg/m^2, $p < 0.0001$) and for patients receiving thyroid hormone therapy for hypothyroidism ($p < 0.0001$; odds ratio [OR] 2.28). Weight change following onset of thyroid hormone therapy was evaluated in a retrospective cohort of 101 adults with newly diagnosed primary hypothyroidism (median TSH ≥18.3 mIU/L, range 10.1–710 mIU/L). The median treatment TSH level was 2.3 mIU/L (range, 0.04–5 mIU/L), and only 52% of patients lost weight, with a mean weight loss of 3.8 ± 4.4 kg. Gender, race, age, initial TSH level, time to normalization of TSH, and initial weight were not associated with changes in weight or BMI after onset of thyroid hormone therapy. Another retrospective analysis compared 245 patients treated with treated hypothyroidism and 162 euthyroid controls. Both groups were similar in height, weight, BMI, and the number of patients with T2DM. The thyroid treated group had more women, Caucasians, and nonsmokers. The average TSH was slightly higher in the treated hypothyroid group compared to controls (median TSH 1.87 vs. 1.55, $p < 0.01$), but there was no significant relationship between TSH and BMI in either group. Thus, it seems unlikely that properly treated hypothyroidism contributes to weight gain.

It has been suggested that abnormalities in thyroid function may be secondary to excess fat mass. However, these changes appear to be functional, since thyroid function becomes normal after weight loss in children and adolescents. In addition, weight loss after bariatric surgery in adults improves or normalizes TSH levels. Chikunguwo and colleagues retrospectively studied thyroid function tests in 86 patients without previous diagnosis of thyroid disorder who underwent gastric bypass or adjustable gastric banding. Before bariatric surgery, 10.5% of subjects had TSH values consistent with subclinical hypothyroidism (defined as elevated TSH with normal free thyroxine). One year after bariatric surgery, all patients experienced significant weight reduction and simultaneous resolution of their subclinical hypothyroidism. The mean BMI change from 49 to 32 kg/m^2 after bariatric surgery was associated with a mean reduction in the TSH level from 4.5 to 1.9 mIU/L. TSH levels correlated positively with BMI ($p < 0.001$) within the BMI range of 30–67 kg/m^2. Of interest, free thyroxine showed no association with BMI and was not significantly influenced by weight loss (Fig. 10.3). Subclinical hypothyroidism is present at the preoperative evaluation for Roux-en-Y gastric bypass in 43% of 503 patients. One year after bariatric surgery, the mean BMI declined from 47 ± 8 kg/m^2 to 33 ± 6 kg/m^2 ($p < 0.001$) and was associated with significant decreases in both TSH (5.8 ± 2.0 to 2.8 ± 1.3 mIU/L, $p < 0.001$) and free thyroxine (15.2 ± 2.1 to 13.9 ± 2.3 pmol/L, $p < 0.001$). Subclinical hypothyroidism resolved in 87% of patients, and this high rate of spontaneous recovery suggests that follow-up alone is sufficient in the majority of patients undergoing bariatric surgery with mild TSH elevations.

10.2.3 Ovaries

Polycystic ovary syndrome (PCOS) is a common endocrine disorder. PCOS affects 6–18% of premenopausal women. Approximately one-half of women with PCOS are reported to have obesity, with increased abdominal and visceral fat. The factors responsible for this association are not fully understood. Excess adiposity is associated with insulin resistance and compensatory hyperinsulinemia and leads to decreased sex hormone-binding globulin synthesis in the liver, and excessive androgen production in the ovaries. These changes lead to a hyperandrogenic state when compared to women of normal weight. There is a significant association between weight gain in early adulthood and symptoms or diagnosis of PCOS. Ollila and colleagues evaluated women with both oligo/amenorrhea and hirsutism at age 31 (n = 126), or diagnosed with PCOS by age 46 (n = 181), as compared to women without PCOS (n = 1577). An increased BMI between the ages of 14 and 31, but not later, was more frequent in all groups of women with isolated oligo/amenorrhea (p = 0.006), oligo/amenorrhea plus hirsutism, (p = 0.001), and PCOS (p = 0.001).

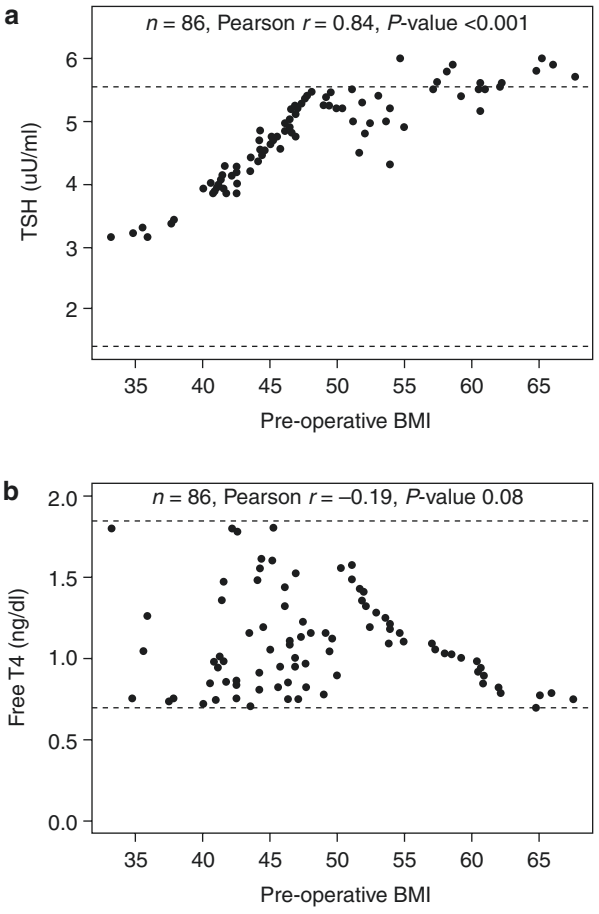
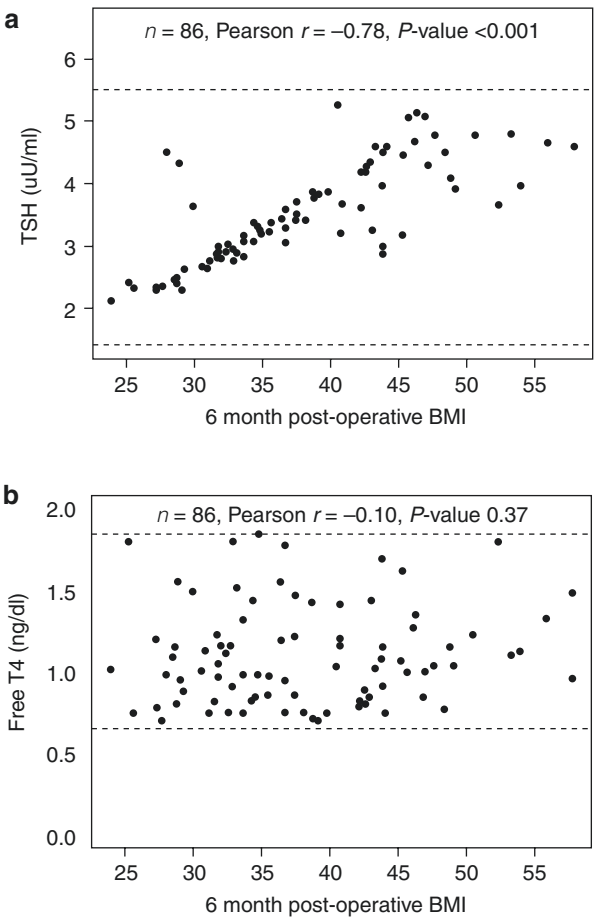


Fig. 10.3 Influence of obesity and surgical weight loss on thyroid hormone levels. Left: Correlation between preoperative BMI and preoperative (**a**) serum TSH and (**b**) free T4 levels. Right: Correlation between BMI 6 months after bariatric surgery and (**a**) serum TSH and (**b**) free T4 levels. Dotted lines represent lower and upper limits of normal range for thyroid hormone concentrations. (Adapted from Chikunguwo et al. 2007; used with permission)

Fig. 3 (continued)



PCOS was significantly associated with increased BMI and higher concentrations of androgens, insulin, and triglycerides.

Cytochrome P450c17α is a key enzyme in the biosynthesis of ovarian androgens and has both 17α-hydroxylase and 17,20-lyase activity. In ovarian theca cells, P450c17α converts progesterone to 17α-hydroxyprogesterone via 17α-hydroxylase, and then converts 17α-hydroxyprogesterone to androstenedione by 17,20-lyase activity. Weight loss using a hypocaloric meal plan in women with PCOS reduces plasma testosterone and glucose-stimulated insulin levels and improves hirsutism. A decline in the waist-to-hip ratio correlates positively with decreases in glucose-stimulated insulin levels and inversely with the decreases in plasma 17-beta-estradiol. Metformin therapy, 500 mg three times a day in women with PCOS, as compared to placebo, significantly reduces the levels of serum insulin, 17α-hydroxyprogesterone, luteinizing hormone, sex hormone-binding globulin, and testosterone, all independent of BMI, although the waist-to-hip ratio decreases with metformin administration ($p = 0.02$). Glintborg and colleagues studied body composition in 90 patients with PCOS randomized to 1 year of metformin (2 g/day),

metformin plus oral contraception (150 mg desogestrel +30 mcg ethinyl estradiol), or oral contraception alone. Treatment with metformin alone or in combination with oral contraception was associated with greater declines in body weight and regional fat mass compared to oral contraception alone. Testosterone levels were comparable between groups.

10.3 Medication-Related Weight Gain: Commonly Used Drugs for Common Diseases

When assessing causes of weight gain, it is important to review the patient's medication list as a number of medications can cause weight gain, including oral diabetes agents, insulin, antidepressants and other mood-altering drugs, antiepileptic drugs, and hormones (Tables 10.2 and 10.3).

Table 10.2 The potential effects of diabetes therapeutic agents on weight change

Drug class	Drug agent(s)	Weight change
Amylin analogs	*Pramlintide*	↓↓
Biguanides	*Metformin*	↓
GLP-1 receptor agonists	*Albiglutide, dulaglutide, exenatide, liraglutide*	↓↓
SGLT-2 inhibitors	*Canagliflozin, dapagliflozin, empagliflozin*	↓
α-Glucosidase inhibitors	*Acarbose, miglitol*	↔
Bile acid sequestrants	*Colesevelam*	↔
DPP-4 inhibitors	*Alogliptin, linagliptin, saxagliptin, sitagliptin*	↔
Dopamine-2 agonists	*Bromocriptine*	↔
Glinides	*Nateglinide, repaglinide*	↑
Sulfonylureas	*Glimepiride, glipizide, glyburide*	↑↑
Insulins	*Aspart, detemir, glargine, glulisine, lispro, NPH, regular*	↑↑
Thiazolidinediones	*Pioglitazone, rosiglitazone*	↑↑

Table 10.3 The potential effects of CNS psychoactive agents on weight change

Drug class	Related to weight gain	Related to weight neutrality or loss
Antidepressants	*Mirtazapine, TCAs, SSRIs (paroxetine)*	*Bupropion, venlafaxine, SSRIs (fluoxetine, sertraline)*
Antipsychotics	*Clozapine, olanzapine, quetiapine, risperidone, thioridazine*	*Aripiprazole, ziprasidone*
Antiepileptics	*Gabapentin, valporate*	*Lamotrigine, topiramate, zonisamide*
Others	*Lithium*	

CNS central nervous system, *SSRIs* selective serotonin reuptake inhibitors, *TCAs* tricyclic antidepressants (i.e., amitriptyline, clomipramine, doxepin, imipramine)

10.3.1 Diabetes-Related Drugs

The risk of developing T2DM and hypertension increases with increasing BMI and WC. BMI and WC are each independently and strongly associated with T2DM, with WC being a stronger risk factor in women than in men. Many patients with obesity have prediabetes or T2DM, and vice versa, and may be treated for metabolic complications with drugs that are weight promoting. Beta-blockers and alpha-blockers prescribed as antihypertensive agents may cause weight gain. Lee and colleagues found that among patients taking beta-blockers and matched to controls, meal-induced thermogenesis, fat oxidation rate, and weekly activity were lower by 50% ($p < 0.01$), 32% ($p = 0.04$), and 30% ($p < 0.01$), respectively. The adjusted mean body weight was significantly higher in these patients who attended either a diabetes clinic (9.2 ± 1.2 kg, $p = 0.0002$) or hypertension clinic (17.2 ± 3.2 kg, $p = 0.004$), compared to patients attending these clinics and not treated with beta-blockers. Weight-neutral agents to control blood pressure would include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers, although more robust studies of the effect of antihypertension drugs on weight change are needed. In addition, there is a high rate of depression in patients with obesity and T2DM, and many psychoactive agents commonly prescribed to improve mood in these patients may promote weight gain. Thus, all patients with prediabetes, T2DM, or obesity should have their medication list carefully reviewed for drugs that can cause weight gain.

Insulin administration is associated with weight gain, for both conventional and intensive insulin therapy. Patients receiving insulin gain approximately 1–3 kg more weight than those receiving other diabetes agents. In the Diabetes Control and Complications Trial, a mean increase in weight of 5.1 kg was seen in the intensive treatment group, versus 2.4 kg in the conventional treatment group. Sulfonylureas and thiazolidinediones are associated with weight gain, whereas metformin use in the Diabetes Prevention Program resulted in a significant 2-kg weight loss in patients with impaired glucose tolerance. Other oral diabetes agents are weight neutral or associated with a small decline in weight (i.e., dipeptidyl peptidase-4 inhibitors, alpha-glucosidase inhibitors, and sodium glucose transport-2 inhibitors). Injectable glucagon-like peptide-1 (GLP-1) receptor agonists used in the treatment of T2DM have been shown to provide improved glycemic control, blood pressure reduction, and weight loss. Patients with T2DM and overweight or obesity should receive instruction in healthy eating patterns and regular physical activity. They should also be treated with diabetes medications that are safe, effective, and weight neutral, or associated with weight loss.

10.3.2 Antidepressants

The Netherlands Study of Depression and Anxiety evaluated data from 2542 adults with major depressive disorder over 6 years of observation, compared to healthy

controls. A current, but not remitted, major depressive disorder was significantly associated with both weight gain and weight loss. Antidepressant use was significantly associated with weight gain both for selective serotonin reuptake inhibitors (OR 1.26, 95% CI, 1.05–1.52) as well as for other antidepressants (OR 1.36, 95% CI, 1.00–1.84) ($p < 0.05$ for both). Compared to patients who lost weight, those who gained weight had lower initial BMI, were younger, had more anxiety disorders, and had poorer quality of mood and reduced appetite as depressive symptoms. Overweight or obesity was found in 72% of a cohort of 127 adult ambulatory patients with depression, studied by Correia and colleagues. A longer duration of depression was associated with significantly higher BMI values and greater fat mass ($p < 0.003$). Weight gain during the observed time of depression was reported in 87% of patients. Antidepressants and benzodiazepines were prescribed in 75% and 72% of patients, respectively, and both were associated with significant weight gain. The tricyclic antidepressants amitriptyline, clomipramine, doxepin, and imipramine are all associated with significant weight gain. In contrast, not all SSRIs have been associated with weight gain. In a randomized study of 284 patients with depression receiving one of three SSRIs (fluoxetine, sertraline, or paroxetine), a significant increase in weight occurred only in the paroxetine group, while no significant weight change was observed in patients taking sertraline or fluoxetine.

10.3.3 Antipsychotics

Both "conventional" first-generation antipsychotics (i.e., thioridazine) and "atypical" second-generation antipsychotics (Table 10.3) can cause significant weight gain, reportedly between 0.8 and 4.4 kg. Antagonism of histamine H1 receptors has been identified as the main cause of second-generation antipsychotic-induced obesity, but the molecular mechanisms are unclear. Blocking hypothalamic H1 receptors by second-generation antipsychotics activates AMP-activated protein kinase (AMPK). During short-term second-generation antipsychotic treatment, hypothalamic H1 receptor antagonism may activate the AMPK-carnitine palmitoyltransferase 1 signaling to rapidly increase caloric intake. During long-term treatment, hypothalamic H1 receptor antagonism can reduce thermogenesis and thus may contribute to fat accumulation by decreasing lipolysis and increasing lipogenesis. Central opioidergic neurotransmission may be implicated in the development of olanzapine metabolic disturbances. Of interest, the addition of naltrexone or placebo to olanzapine in a randomized, double-blind pilot study did not result in BMI differences between groups. However, subjects taking naltrexone plus olanzapine had a significant decrease in fat, increase in FFM, and a trend toward improvement in homeostatic model assessment of insulin resistance, compared to controls. In another randomized, double-blinded, placebo-controlled trial, melatonin was found to be effective in attenuating adverse metabolic effects of second-generation antipsychotics in patients with bipolar disorder but not with schizophrenia. Significant beneficial outcomes with melatonin were seen on fat mass and diastolic blood

pressure, compared to placebo. Second-generation antipsychotics also seem to induce a hypometabolic state. Adolescents taking olanzapine, quetiapine, or risperidone monotherapy were analyzed using anthropometric measurements, bioelectrical impedance analysis, and indirect calorimetry to measure REE. Patients gained 10.8 ± 6.2 kg (60% as fat mass) and increased WC by 11.1 ± 5.0 cm after only 1 year of treatment. The REE/kg body mass ratio decreased ($p = 0.027$), and the REE/percentage FFM ratio increased ($p = 0.007$) during treatment. This could explain, at least in part, the changes in weight and body composition observed in these patients. Taken together, these findings support a centrally mediated imbalance during use of mood-altering drugs that can lead to changes in weight and body composition, as well as adiposopathy and adverse metabolic clinical outcomes.

10.3.4 Antiepileptics

The antiepileptic drugs valproic acid and carbamazepine are also used in the management of bipolar disorder and are associated with weight gain. Gabapentin is commonly used for treatment of neuropathic pain and can also cause weight gain, whereas topiramate and zonisamide do not promote weight gain. Shapiro and colleagues reported on 47 adolescent patients with an average BMI of 30.2 kg/m^2 who were first prescribed topiramate or zonisamide and subsequently had the addition of at least one mood-altering drug. Of these patients, topiramate was initially prescribed in 91% of adolescents due to its safety profile, and 92% were later prescribed an antipsychotic (e.g., aripiprazole, quetiapine, or risperidone). Anticonvulsant dosage was associated with an average decline in BMI of 3.2–6.1 kg/m^2 for every 6 months of treatment in patients with a baseline BMI $\geq$25 kg/m^2, and weight reduction was not statistically different between patients taking topiramate or zonisamide.

10.3.5 Gonadal hormones

Many progestin-only contraceptives are long acting and cost effective in preventing pregnancy, but concerns about weight gain can deter initiation, or cause early discontinuation of their use. In a review of contraceptive use studies, weight change for women taking progestin-only contraceptives generally did not differ significantly from their comparison contraceptive group, with a mean weight gain <2 kg for most studies of 1-year duration. However, three studies showed significant differences for progestin-only contraceptives compared to women not using a hormonal method of contraception. Three-year weight gain is greater with depot medroxyprogesterone acetate (DMPA) use compared to women using a nonhormonal IUD. DMPA users also have significantly greater percent increases in body fat and a decrease in lean body mass. There is a 1 year greater increase in weight with DMPA use, compared

to women using an IUD contraceptive, with the weight increase due to an increase in fat mass. In contrast, women who used DMPA postpartum do not differ from women choosing bilateral partial salpingectomy sterilization in either weight or percent body fat at 1-year follow-up. About half the women using DMPA return to their prepregnancy weight. However, the other half of DMPA users gain weight, with a higher prepregnancy BMI associated with postpartum weight gain.

Serum testosterone level decreases in men by 0.4–2% per year after the third decade of life. In addition to increasing age, obesity has been associated with decreased serum testosterone. There is evidence that low testosterone levels promote fat accumulation, suggesting a bidirectional relationship between adiposity and testosterone. A total of 3369 community-dwelling men aged 40–79 years were evaluated as part of the European Male Aging Study and categorized as eugonadal (n = 1909), incident secondary hypogonadal (n = 140), or persistent secondary hypogonadal (n = 123). Incident secondary hypogonadism is predicted by a BMI of $\geq$30 kg/m^2 (OR 2.86, $p < 0.0001$), weight gain (OR 1.79, $p = 0.011$), and increased WC (OR 1.73 for WC 94–102 cm, $p = 0.026$ and 2.64 for WC $\geq$102 cm, $p < 0.0001$). Late-onset hypogonadism occurs in middle-aged and elderly men and is defined by hypogonadal symptoms in the presence of low testosterone levels. In the European Male Aging Study, 63 men (2.1%) were classified as having moderate or severe late-onset hypogonadism. Only men with severe late-onset hypogonadism showed significant associations with WC, insulin resistance, and dysmetabolic syndrome, although men with low testosterone levels only had lesser magnitudes of association for the same end points. Androgen deprivation therapy is employed in men with locally advanced, recurrent, and metastatic prostate cancer and has been prospectively shown to cause decreased lean muscle mass, increased fat mass, weight gain, increased cholesterol and triglycerides, and insulin resistance. Mean increases in body weight and WC after 1 year of androgen-deprivation therapy have been reported as 2.9% and 3.0%, respectively. Visceral and subcutaneous fat (measured by computerized tomography) both increase by >20%, although the increase in subcutaneous fat is significantly greater than that measured in visceral fat. Studies in men taking androgen-deprivation therapy are needed. Physical activity is associated with significantly improved health and disease-specific quality of life in men taking androgen-deprivation therapy. However, physical activity does not have a beneficial effect on weight, WC, lean mass, fat mass, blood pressure, or lipids.

10.4 Conclusion

Patients inquire about, and physicians and other health-care providers often screen for, endocrine-related disorders as a cause of weight gain in persons who have overweight or obesity. Endocrine disorders may be associated with modest weight gain, as seen in subclinical hypothyroidism or subclinical hypercortisolism, but they rarely are the sole culprit for marked or continued weight gain. Cushing's syndrome is rare and has an unmistakable phenotype. Hypothyroidism is common but rarely

results in significant weight gain, even in patients with profound hypothyroidism. These endocrine disorders, Cushing's syndrome and myxedema, are usually quickly diagnosed and properly treated. The more difficult scenario is the patient with T2DM who has overweight or obesity and may have anxiety and depression. Polypharmacy is common in these patients, and they may be taking drugs for diabetes, depression, anxiety, and pain that promote weight gain. Behavioral change is critical to the prevention and treatment of patients who have overweight or obesity. However, a focus solely on modifying individual behaviors for healthy eating and increased physical activity may have had limited success if physicians and healthcare providers are not aware of the genetic variability between individuals in energy metabolism and the effect that commonly prescribed medications can have on weight change.

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