Secondary causes of obesity

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While the rising epidemic of obesity is primarily attributed to sedentary lifestyle, poor dietary habits and the aging of the population, secondary causes of obesity generally go undetected and untreated. These include endocrinological disorders, such as Cushing's syndrome, polycystic ovary syndrome, hypogonadism and hypothyroidism, as well as genetic, syndromic and drug-related obesity. We present an overview of the major disorders associated with obesity, highlighting the pathophysiologic mechanisms and discussing diagnostic and treatment strategies that are most helpful to practicing physicians in recognizing and treating these generally underdetected and undertreated disorders.

During the past few decades, prevalence of obesity has dramatically increased in the Western world, including the USA where obesity has currently reached epidemic proportions. A comparison of data from two National Health and Nutrition Examination Surveys (NHANES) has shown that among US adults, the prevalence of obesity increased from 15% (in the 1976–1980 survey) to 32.9% (in the 2003–2004 survey) [1]. Data from the 2003–2004 survey estimate that approximately 66% of US adults are overweight or obese and 17.1% of US children and adolescents are also overweight [1]. This sharp increase in the prevalence of obesity correlates with a proportional increase in obesity-associated comorbidities, such as Type 2 diabetes, hypertension and cardiovascular disease (CVD) [2], and a significant rise in healthcare costs related to obesity [3]. The economic burden of obesity in the USA was estimated to be US$117 billion in 1998, with obesity accounting for approximately 5.7% of the US National Health expenditure [3].

The relatively rapid and dramatic increase in the prevalence of obesity has been largely attributed to a changing lifestyle that promotes increased caloric intake and reduced physical activity. A high-fat diet, excessive consumption of sugar-sweetened beverages and increased fast food intake might all contribute to the continuing increase in prevalence of obesity [4].

Although most cases of weight gain are indeed related to increased caloric intake and sedentary lifestyle, obesity can also be secondary to known and possibly treatable neuroendocrine or genetic disorders that affect appetite, metabolism, energy balance and fat distribution (**Box 1**). Although rare, these conditions should be recognized by physicians and specific therapeutic strategies should be planned in conjunction with diet and exercise.

In this review, we provide the readers with a general overview of the secondary causes of obesity, highlighting the pathophysiology, the clinical diagnosis and the therapeutic options of each disorder.

Obesity is a state of excessive body weight associated with adverse health risks such as diabetes, hypertension, hyperlipidemia and coronary artery disease. In 1997 and 1998, The WHO and the National Heart Lung and Blood Institute of the National Institute of Health advocated the use of a specific BMI threshold of 30 to diagnose obesity and 25 to diagnose overweight [5,6]. The BMI is calculated by dividing a person's weight in kg by height in m^2.

Furthermore, it appears that fat distribution plays a key role in determining the associated health risks. Central or android obesity is associated with greater risk of adverse health effects than lower-body or gynecoid obesity [7]. Therefore, waist circumference measurement has been a useful clinical tool in risk stratification of overweight in moderately obese patients (BMI 25–35). A waist circumference greater than 40 inches (102 cm) in men and 35 inches (88 cm) in women is linked to higher CVD risks and should lead to more aggressive weight reduction strategies in overweight patients.

Interpretation of BMI values may also change with ethnicities. For example, android obesity leading to increased cardiovascular risk is clearly present in Asian individuals with lower BMI (not in overweight and obesity categories), suggesting a lower BMI cut-off for definition of obesity in this population [8].

Keywords: endocrinologic obesity, genetic obesity, obesity, overweight, secondary obesity, syndromic obesity

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Box 1. Endocrine and genetic causes of obesity.

Endocrine causes

- Hypothyroidism
- Cushing disease
- Polycystic ovaries
- Growth hormone deficiency
- Hypothalamic obesity
- Hypogonadism
- Insulinoma
- Pseudohypoparathyroidism

Genetic causes

Monogenic obesity:

- Leptin and leptin receptor deficiency
- POMC deficiency
- Melanocortin Receptor 4 deficiency
- Prohormone convertase deficiency
- BDNF and TrkB insufficiency
- SIM 1 insufficiency

Syndromic obesity:

- Prader–Willi syndrome
- Bardet–Biedl syndromes
- Beckwith–Wiedemann syndrome
- Alstrom–Hallgren syndrome
- Carpenter syndrome
- Cohen syndrome

Pathophysiology of obesity

The development of obesity requires a period of positive energy balance where energy intake exceeds energy expenditure, manifesting clearly in obese individuals with high caloric intake and sedentary lifestyle. Energy expenditure is divided into basal metabolic rate, energy expended in activity and thermic effect of food. Moreover, to maintain energy balance, the organism should be able to assess its own energy stores, the caloric content of the diet and the current balance status of the body, and be able to adjust hormone levels, energy expenditure and consumption behaviors accordingly. A defect at any energy balance level may result in positive balance and obesity, as seen in most cases of secondary obesity (**Figure 1**).

Endocrine causes of obesity

Cushing's syndrome

Cushing's syndrome results from prolonged exposure to glucocorticoid excess deriving from four potential sources: pituitary tumors (Cushing's disease), adrenal tumors, ectopic adrenocorticotropic hormone (ACTH) secretion and, most commonly, exogenous glucocorticoids, including oral, topical or inhaled steroids.

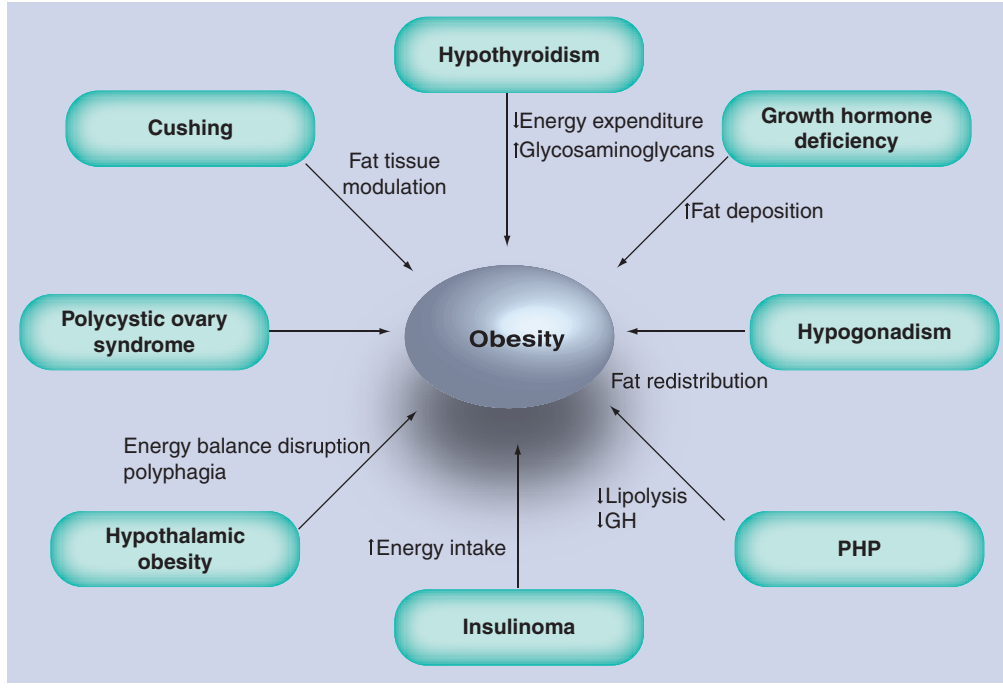
At a physiological level, the principal glucocorticoid, cortisol, contributes significantly to the regulation of protein, carbohydrate, lipid and nucleic acid, enhancing the production of blood glucose by antagonizing the secretion and action of insulin, increasing peripheral protein breakdown and enhancing the activation of lipoprotein lipase in adipocytes, which in turn increases fat accumulation [9]. Glucocorticoids are also required for the differentiation of adipose stromal cells to mature adipocytes. The action of cortisol on adipose tissue varies in different parts of the body, decreasing peripheral adipose tissue mass and expanding abdominal and interscapular fat.

Furthermore, the highly expressed 11 β-hydroxysteroid-dehydrogenase-1 in omental adipose tissue is believed to enhance the local effect of cortisol on adipose tissue by converting inactive cortisone to active cortisol [10].

Hypercortisolism in Cushing's syndrome results in central obesity, with fat accumulation in the face (moon face), neck, dorsocervical area (buffalo hump), supraclavicular area (fat pads), retroorbital space (exophthalmos), trunk and abdomen, with sparing or wasting of the extremities, characterizing the typical central fat distribution of the syndrome [11]. In addition to the gradual obesity that develops in 80–90% of individuals, patients with Cushing's syndrome may present with hypertension, impaired glucose tolerance, proximal muscle weakness, thinning of the skin, increased tendency to bruise, red or violacious striae, hypokalemia, osteoporosis with vertebral compression fracture or aseptic necrosis and menstrual irregularities with signs of androgen excess in women. Hyperpigmentation in this context reflects significantly elevated ACTH levels, favoring the etiologic diagnosis of ectopic ACTH secretion, and to a lesser degree Cushing's disease. Children with Cushing's syndrome characteristically present with abnormal weight gain and poor linear growth [12].

A widely used screening test for Cushing's syndrome is the overnight 1 mg low-dose dexamethasone suppression test where at 8 am the cortisol value is expected to be lower than 2 µg/dl (55 nmol/l) in normal subjects who had received dexamethasone 1 mg at 11 pm. However, owing to relatively high rates of false-negative and false-positive results, a 24 h urine-free cortisol test is considered a more accurate diagnostic approach, followed if necessary, by late-evening plasma or salivary cortisol level [13,14]. Acute or chronic

Figure 1. Endocrinologic etiologies of obesity and related pathophysiology.



PHP: Pseudohypopparathryoidism.

illnesses, depression and alcohol abuse can result in hypercortisolism or pseudo-Cushing's syndrome, sometimes making the distinction more difficult and challenging.

The treatment of Cushing's syndrome should act to target the etiology of excessive glucocorticoids in specific patients.

Hypothyroidism

Primary hypothyroidism is a very common disease worldwide. In the UK, the Whikham survey revealed an incidence of hypothyroidism of 4.1/1000/year in women and 0.6/1000/year in men [15,16]. Similarly, in the NHANES III in the USA, hypothyroidism was found in 4.6% of the 13,344 people screened without known thyroid disease [17]. Marked female preponderance and autoimmunity were uniformly noted in these populations [15–17]. The prevalence of hypothyroidism can be more common in iodine-deficiency regions. Other common etiologies of hypothyroidism include iatrogenic causes such as postthyroidectomy and postradioiodine hypothyroidism.

In adults, thyroid hormone plays a major role in metabolism by increasing food intake and subsequently, the thermic effect of food, accelerating metabolic rates and enhancing thermogenesis, leading to a net increase in energy expenditure [18]. Thyroid hormone deficiency slows metabolism, resulting in a decrease of resting energy expenditure, oxygen consumption and utilization of substrates. Reduced thermogenesis is reflected in the classical cold intolerance of hypothyroid patients. The effect of thyroid hormone deficiency on appetite and energy intake is not well known, however the decrease in energy expenditure explains the slight net gain in energy stores and adipose tissue observed in these patients. Another mechanism contributing to weight gain in hypothyroidism is the accumulation of fluid rich in glycosaminoglycans. However, marked obesity is not characteristic of hypothyroidism.

In addition to modest weight gain, hypothyroidism is clinically characterized by fatigue, cold intolerance, joint aches, constipation, depression, dry skin, hair loss and menstrual irregularities. Physical examination may reveal firm goiter, hypertension, bradycardia, periorbital swelling, coarse hair, dry skin, and delayed relaxation of the deep tendon reflexes. Laboratory clues to hypothyroidism include normocytic anemia, hypercholesterolemia, hyponatremia and elevated creatinine phosphokinase.

The measurement of serum thyroid-stimulating hormone (TSH) level is currently the most sensitive test for screening for hypothyroidism.

In view of the high prevalence of the disease and the simplicity of the screening tool, it is recommended that obese patients should be screened for hypothyroidism. Most symptoms reverse shortly after administration of synthetic thyroid hormone replacement.

Polycystic ovaries syndrome

Polycystic ovaries syndrome (PCOS) is one of the most common female reproductive disorders, affecting 5–10% of premenopausal women [19]. The key clinical features of PCOS are menstrual irregularities (due to oligomenorrhea or amenorrhea and hyperandrogenism), causing hirsutism, acne and male-pattern hair loss with elevated serum androgen levels [20]. Polycystic ovaries, infertility, insulin resistance and obesity are other classic associated manifestations of the syndrome. Studies have shown that approximately 50% of women with PCOS are obese [21]. The pathophysiologic link between PCOS, insulin resitance and obesity is not clearly understood. Hyperinsulinemia, especially in the presence of obesity, increases androgen levels by stimulating androgen biosynthesis in the ovarian theca cell and by suppressing sex hormone binding globulin (SHBG) production by the liver. On the other hand, obesity by itself may favor ovarian hyperandrogenism in a subset of PCOS women [22,23].

Weight loss and insulin-sensitizing agents, such as metformin and thiazolidinediones, have been associated with improvement of hyperandrogenism and metabolic parameters of PCOS, including restoration of menses [24].

Growth hormone deficiency

Growth hormone (GH) deficiency is the most common hormonal deficits observed in pituitary disease, almost constantly in the setting of hypopituitarism. GH plays significant roles in regulating energy expenditure, body composition, bone mineral density, lipid metabolism and cardiovascular function. Notably, GH inhibits lipoprotein lipase, increases hormone-sensitive lipase, and stimulates adipocytes lipolysis. [25]. GH enhances protein synthesis and increases muscle and bone mass. GH deficiency in adults is associated with decreased muscle mass, increased truncal fat deposition and reduction of total body water, with a net weight increase of 3.6–7.5 kg of body weight compared with normal subjects [26].

The diagnosis of GH deficiency in adults is usually established with the history of pituitary or hypothalamic disease with panhypopituitarism, and either a subnormal serum insulin-like growth factor-1 concentration or a subnormal serum GH response to a potent stimulus such as insulin-induced hypoglycemia or the combination of arginine and growth hormone-releasing hormone (GHRH).

Therapy with GH replacement has demonstrated efficacy in restoring normal body fat distribution and increasing resting energy expenditure, along with variable improvements in other cardiovascular and metabolic parameters [27,28].

Hypothalamic obesity

Obesity is commonly observed in patients with hypothalamic tumors, trauma, inflammation, or after hypothalamic surgery or radiotherapy. Weight gain is thought to result from the injury of the ventromedial hypothalamic nucleus. Its major role is to integrate metabolic information regarding nutrient stores and food availability. Damage to these areas leads to hyperphagia, decreased metabolic rate, autonomic imbalance and GH deficiency, all of which result in progressive obesity [29,30]. An associated alteration in corticosteroid metabolism may also contribute to weight gain in hypothalamic obesity, by enhancing endogenous or exogenous glucocorticoids effect.

Clinically, patients with hypothalamic obesity might present with headache, vomiting, visual disturbances, diabetes insipidus, hypogonadism, hypothyroidism, adrenal insufficiency hypothermia, hyperthermia or neurologic symptoms.

Obesity occurs in approximately 50% of children treated surgically for craniopharyngeoma [31].

Patients at high risk of hypothalamic obesity should be indentified and counseled regarding life therapeutic changes to prevent weight gain together with specific hormone replacement as indicated.

Hypogonadism

Gonadal steroids play a determinant role in body fat distribution, as reflected by the typical gender-related body fat changes that occur at the onset of puberty.

Androgens contribute significantly to fat metabolism and body fat composition [32]. Testosterone inhibits uptake of triglycerides and promotes lipid mobilization from visceral fat [33]. In addition, testosterone levels are inversely associated with visceral fat mass, which may explain the increased visceral obesity with age in men.

Androgen deficiency has been classically associated with obesity and metabolic syndrome [34], whereas testosterone therapy has showed decreases in visceral adiposity and improvements in glycemic control, insulin resistance and cholesterol [35–37].

Of note, obesity may decrease the serum concentration of SHBG, thereby decreasing the serum total testosterone concentration without normally lowering the free testosterone concentration. The binding abnormality is proportionate to the degree of obesity and is corrected by weight loss [38].

Similarly, menopause is often associated with decreased lean body mass with increased visceral fat and visceral fat–subcutaneous fat ratio, with or without weight gain [39–41]. The fat redistribution in postmenopausal women is thought to be the result of the loss of estrogen and progesterone and the relatively rapid decline in GH. Predisposition to central obesity in postmenopausal women is associated with metabolic abnormalities such as increased cholesterol levels and plasma glucose [39,40], and may therefore directly affect the cardiovascular risk.

Despite the lack of change in body weight with the use of hormonal replacement therapy, estrogen replacement has been linked to the reversal of abdominal obesity in postmenopausal women as well as improvement of lean body mass [42].

Insulinoma

Insulinoma is an extremely rare disease characterized by tumoral excessive insulin secretion, manifesting clinically by frequent hypoglycemias, inconstantly associated with neuroglycopenic and autonomic symptoms. Insulinomas are associated with obesity in 18–39% of individuals [43]. Weight gain in these patients is believed to be related to excessive caloric intake in order to avoid hypoglycemia and is usually reversible after surgical treatment.

Pseudohypoparathyroidism

Pseudohypoparathyroidism type 1a (PHP1a) is an autosomal dominant disease due to maternal transmission of a mutation of the *GNAS1* gene, leading to an inability to activate adenyl cyclase and therefore causing target-organ unresponsiveness to multiple hormones, including parathyroid hormone (PTH), TSH, luteinizing hormone, follicle-stimulating hormone and GHRH. Multiple pathways affected by *GNAS1* mutation might contribute to the development of obesity: reduced lipolytic response to epinephrine (secondary to decreased intracellular cAMP levels), accelerated differentiation of fibroblasts to adipocytes and GH deficiency [44–47]. Patients have a classical presentation, known as Albright hereditary osteodystrophy (AHO), characterized by round faces, short stature, short fourth metacarpal bones, obesity, subcutaneous ossifications and developmental delay, in addition to the hyperphosphatemia and hypocalcemia owing to PTH resistance at the renal tubule, along with secondary hyperparathyroidism and hyperparathyroid bone disease (osteitis fibrosa).

Paternal inheritance of the mutation, which usually leads to the AHO alone without PTH abnormalities (pseudopseudohypoparathyroidism), might not be as strongly associated with obesity as PHP1a [48].

Genetic causes of obesity

Genetic susceptibility to obesity

Body weight appears to be determined through an interaction of genetic, environmental and psychosocial factors. The genetic contribution to body weight is thought to work through susceptibility genes and heritability estimates of 40–70% have been constantly reported in family studies and investigations of twins and adopted children [49–51]. If both parents are obese, approximately 80% of their offspring will also be obese. If only one parent is obese, the likelihood of obese offspring falls to 10%. Human obesity appears to be polygenic in the majority of cases.

Single-genes causes of obesity

During the past few decades, intensive research led to the identification of several genes involved in signaling between peripheral sites and the hypothalamic center of satiety and hunger, such as leptin, pro-opiomelanocortin (*POMC*), prohormone convertase 1 and melanocortin 4 receptor (*MC4R*) genes. In most cases, these gene mutations lead to abnormal eating behaviors followed by the development of severe early-onset obesity, which is usually not associated with other abnormal features. Obesity based on a mutation of one gene product is called monogenic obesity.

Leptin & leptin receptor deficiency

Produced mostly by adipose tissue, leptin is a hormone that plays a determinant role in signaling the brain regarding the quantity of stored fat

and, with respect to food intake, acting in the hypothalamus to reduce the production of neuropeptide Y2, one of the most potent stimulators of appetite [52,53].

While leptin levels were found to be elevated in most obese individuals, suggesting possible leptin resistance, congenital leptin and leptin-receptor deficiencies due to mutations in the leptin or leptin-receptor genes have been described in few families, mostly from Pakistan, Turkey and Algeria [54–56]. Clinically, these patients present with profound hyperphagia and early-onset obesity, as well as hyperinsulinemia, hypothalamic hypothyroidism and hypogonadotropic hypogonadism. Therapy with physiologic doses of leptin resulted in a dramatically decreased food intake and substantial reduction in weight and fat mass [57,58].

POMC deficiency

POMC is the precursor of ACTH, lipotropin, α-melanocyte-stimulating hormone (α-MSH), β-MSH and endorphin. Bioactive peptides derived from this prohormone are generated in neurons of the hypothalamus and act as endogenous ligands for the MC4R, a key molecule in appetite control and energy homeostasis. Congenital POMC deficiency has been described in families, with clinical characteristics of isolated ACTH deficiency (MC2R signaling deficiency), hyperphagia with severe early-onset obesity (MC3R and MC4R signaling deficiency) and altered skin and hair pigmentation (MC1R signaling deficiency), manifesting with red hair in patients of Caucasian origin [59]. Heterozygous parents are asymptomatic, suggesting an autosomal recessive mode of inheritance.

MCR4 deficiency

Of the five known melanocortin receptors, MC4R has been particularly linked to energy balance control in rodents and is thought to mediate most of the anorectic effects of leptin [60,61]. Mutations of this receptor in humans represent the most common cause of monogenic obesity because they are detected in 1–2.5% of obese patients and almost 6% of adults with early-onset severe obesity [62,63]. More than 30 different mutations of *MC4R* have been identified. Homozygous forms are associated with more pronounced obesity.

Clinical spectrum of MC4R includes early hyperphagia leading to obesity, along with increase in bone mass. Nonetheless, obese adult carriers of functionally relevant *MC4R* mutations do not specifically present with binge-eating disorder or a history of early-onset obesity [62]. The onset and severity of the obesity in the carriers is related to the functional severity of the *MC4R* mutations. Although there is no specific therapy at this time for MC4R deficiency, research is open to potential development of MC4R agonists in heterozygote forms of the disease [64].

Syndromic obesity

Severe obesity is a characterisitic feature of many congenital and genetic disorders, such as AHO, Alstrom–Hallgren syndrome, Bardet–Biedl syndrome, Beckwith–Wiedeman syndrome, Carpenter syndrome, Cohen syndrome and Prader–Willi syndrome (PWS), the latter being one of the most common syndromic forms of obesity in children [65]. In addition to being overweight, children with genetic syndromes associated with obesity typically have characteristic physical findings, including dysmorphic features, developmental delay and mental retardation.

Prader–Willi syndrome

PWS is a congenital neurodegenerative disorder caused by genetic abnormalities of the long arm of chromosome 15(q11–13), usually secondary to the deletion of paternal DNA, leading to the lack of the *SNRP* gene, which occurs sporadically [66]. Clinically, PWS results in hypotonic infants and later in insatiable obese, mildly retarded, behaviorally disturbed adolescents and adults [67]. Most patients have reduced GH secretion and hypogonadotropic hypogonadism, suggesting hypothalamic–pituitary dysfunction [68,69]. Genetic testing usually confirms the clinical diagnosis. There is no effective treatment for most of the problems associated with PWS. Nevertheless, encouraging results have been observed with the early administration of GH, resulting in accelerated growth and decreased body fat; sex hormone replacement may also be beneficial [69,70]. Obesity management is crucial in the care of the patients with PWS; limiting access to food through close supervision and physical barriers is usually recommended.

Iatrogenic causes of obesity

Drugs

A review of medications is essential in the assessment of obese patients as several drugs are known to be associated with weight gain.

Anti-diabetic medications

In the UK Prospective Diabetes Study (UKPDS), treatment of diabetic patients with insulin and sulfonylureas, and not metfomrin, resulted in an average weight gain of 4.8 kg in 3 years [71]. The effect of insulin is usually associated with increased hunger and appears to be dose-dependent [72]. A potential explanation of the weight gain with insulin is the improved utilization of calories through a decrease in glycosuria.

Thiazolidinediones use is also classically associated with modest weight gain, with preferential distribution of fat in the subcutaneous areas and around the hips [73].

Diabetic patients treated with insulin or sulfonylureas or thizolidinediones should be counseled regarding lifestyle changes necessary to avoid weight gain.

Centrally acting medications

Antipsychotics, antidepressants and antiepileptics can increase body weight, probably through their effect on the monoamines in the CNS. Among newer neuroleptic medications, clozapine and olanzapine have been associated with an average weight gain ranging between 3–4.4 kg and an increased risk of diabetes and dyslipidemia [74,75]. Moreover, schizophrenia has been associated with an increased risk of metabolic disturbances and diabetes; this link is poorly understood, with a low attribution to the role of antipsychotic medication [76].

The antidepressants amiryptilin and paroxetine have specifically been implicated in weight gain. Carbamazepine, gababpentin and valproates are anticonvulsants that can cause weight gain as well. Weight-reducing or weight-neutral alternatives should always be considered when possible in overweight or obese subjects.

Smoking cessation

Smoking cessation has been traditionally linked to a 3–5 kg average weight gain, which is thought to be at least in part due to nicotine withdrawal [77]. The potential mechanisms of weight gain include increased caloric intake, decreased resting metabolic rate, decreased physical activity and increased lipoprotein lipase activity. Therefore, close monitoring of body weight and promoting lifestyle changes should be part of smoking cessation programs. The use of bupropion and nicotine replacement, particularly nicotine gum, might be helpful in preventing weight gain in this vulnerable population [77].

Expert commentary

In addition to assessing the degree of obesity and screening for the associated comorbidities and cardiovascular risk factors, the evaluation of obese patients should include screening for potentially treatable endocrine, neurologic or genetic conditions.

Symptoms of hypothyroidism, hypogonadism, glucocorticoid excess, PCOS or hypothalamic and pituitary deficits should direct physicians towards a possible underlying endocrine or hypothalamic disorder. The presence of hyperphagia and early severe obesity, along with a positive family history of early-onset obesity, supports a genetic diagnosis. The presence of dysmorphic features with massive obesity in young patients suggest syndromic obesity. Medications should always be reviewed and alternatives to weight gain-associated drugs should be offered.

Nonetheless, secondary obesity is rare and environmental factors on a genetic predisposition background represent the most common etiology of obesity. Therefore, lifestyle changes including dietary modification and increased

Executive summary

- Secondary causes of obesity are rare and can be divided into endocrinological, genetic and iatrogenic etiologies.
- Endocrinologic diseases leading to obesity include hypothyroidism, Cushing's syndrome, polycystic ovaries syndrome, hypogonadism, growth hormone deficiency, hypothalamic diseases and pseudohypoparathyroidism.
- Early-onset obesity with abnormal eating behavior are suggestive of monogenic obesity, such as leptin deficiency, MCR4 deficiency and pro-opiomelanocortin deficiency.
- Prader–Willi syndrome is characterized by severe obesity in early age with insatiability, mild mental retardation and hypogonadism.
- Several centrally acting medications and antidiabetic agents can be associated with obesity.
- Physicians should recognize potentially treatable secondary causes of obesity.

physical activity remain the cornerstone of management of obesity, even in several of the secondary causes of obesity such as drug-induced obesity, postmenopause, PCOS, hypothalamic obesity and syndromic obesity.

Future perspective

Although endocrinologic diseases and syndromes associated with obesity are well established and described entities, genetic causes of overweight and obesity remain poorly known and are currently the focus of intensive research at different phases of development. Identifying the genetic basis of obesity will certainly open the door to novel therapeutic agents that could potentially curb the escalating epidemic of obesity.

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