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Endocrine Disorders Associated with Obesity

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Annotation: Several endocrine disorders, including diabetes, insulinoma, Cushing syndrome, hypothyroidism, polycystic ovarian syndrome, and growth hormone deficiency, are associated with obesity. The mechanisms underlying the development of obesity vary according to the abnormalities of endocrine function. The primary actions of insulin, glucocorticoids (GCs), thyroid hormone, and growth hormone are associated with energy metabolism in the liver, muscle, adipose tissue, and other tissues. This chapter describes the pathogenesis of obesity and metabolic dysfunction associated with excess insulin or GCs and the deficiency of thyroid hormone or growth hormone.

Introduction

Hyperinsulinemia, hypercortisolism, hypothyroidism, and growth hormone deficiency are often associated with obesity. Insulin is a potent anabolic hormone, and treatment with insulin or some anti-diabetic drugs results in weight gain through direct effects on adipogenesis and lipid storage. Insulinoma is a rare cause of hyperinsulinism associated with hypoglycemia, hunger, and rapid weight gain. Excessive glucocorticoid (GC) exposure in Cushing syndrome results in central obesity, sarcopenia, osteoporosis, hypertension, and dyslipidemia. The local production of active GCs in adipose tissue by 11 beta (β)-hydroxysteroid dehydrogenase type 1 has been implicated in obesity, insulin resistance, and hypertension. Hypothyroidism increases body weight by decreasing thermogenesis and increasing fluid retention and the interstitial accumulation of glycosaminoglycans. Hypothyroidism also increases cholesterol synthesis and impairs insulin sensitivity. Growth hormone deficiency in adults decreases lean tissue mass and increases fat. The focus of this chapter will be on putative mechanisms linking obesity to excessive exposure to insulin and GCs and thyroid and growth hormone deficiencies.

Insulin is secreted by the pancreatic β cells of the islets of Langerhans in response to elevated blood glucose levels during the postprandial period, potentiated by the effects of amino acids and fatty acids and incretin hormones produced in the gastrointestinal tract [1]. Insulin is a key anabolic hormone responsible for promoting glycogen storage in the liver and skeletal muscle, as well as triglyceride storage in adipose tissue and the liver. Following secretion, insulin binds to the insulin receptor (IR), which consists of two alpha (α) subunits and two β subunits, which form a hetero-tetrameric complex. Insulin binds to the extracellular (α) subunits, transmitting a signal across the plasma membrane that activates the intracellular tyrosine kinase domain of the β subunit. Insulin binding to the external component of its receptor results in the activation of receptor tyrosine kinase [2]. Once activated, the IR can phosphorylate a number of substrate proteins that initiate downstream signaling pathways. Intracellular substrates of IR tyrosine kinase include IR substrate proteins, Shc, Cbl, APS, and Grb2-associated binder-1 (Gab-1). The core cellular processes downstream of the insulin signaling network involve the phosphatidylinositol 3-kinase (PI3-kinase) and the mitogen-activated protein kinase (MAPK) pathways [3].

While a pathway leading to activation of MAPK promotes cell division, protein synthesis, and cell growth by phosphorylating transcription factors leading to activation of gene expression, the regulatory roles of insulin in energy metabolism are largely mediated by the PI3-kinase pathway [4,5]. The major metabolic pathways stimulated by insulin are glycolysis, glycogen synthesis, lipogenesis, and protein synthesis. In contrast, insulin inhibits gluconeogenesis, glycogenolysis, lipolysis, fatty acid oxidation, and protein degradation. The PI3-kinase pathway also regulates glucose uptake through the translocation of the glucose transporter GLUT4 to muscle and fat cell membranes [6]. Insulin

stimulates glycogen synthesis, while it downregulates glucose production by suppressing gluconeogenesis and glycogenolysis in the liver. Insulin increases the rate of glycolysis by increasing glucose transport and the activities of hexokinase and 6-phosphofructokinase in muscle. Glycogen synthase, the key regulating enzyme for glycogen synthesis, is activated by insulin. During fasting, the decrease in insulin and increase in counter-regulatory hormones, such as glucagon, epinephrine, GCs, and growth hormone, stimulate glycogenolysis and gluconeogenesis in the liver, leading to glucose release to ensure adequate fuel supply to the brain and other vital organs. Insulin also plays an important role in lipid metabolism. Insulin decreases lipolysis in adipose tissues by inhibiting hormone-sensitive lipase activity, thereby lowering plasma fatty acid levels [7]. Insulin resistance attenuates lipolysis, especially that of upper-body or visceral fat, in obesity. Thus, individuals with obesity with a predominance of intra-abdominal fat have higher rates of fatty acid mobilization and greater resistance to the anti-lipolytic effects of insulin when compared with the corresponding parameters in individuals with excess lower body fat [8,9]. Insulin also stimulates *de novo* lipogenesis from glucose in the liver and adipose tissue. Insulin is a strong activator of lipogenesis through the increased expression of lipogenic enzymes such as fatty acid synthase and acetyl-CoA carboxylase. Insulin stimulates the re-esterification of fatty acids in adipose tissues and the liver in the form of triglycerides. Insulin also increases lean and muscle mass by suppressing proteolysis and enhancing protein synthesis [10]. Obesity and diabetes are closely linked and are increasing worldwide. Because most patients with type 2 diabetes (T2D) are overweight or obese at the time of diagnosis, iatrogenic weight gain is an important clinical issue that can hinder successful management. Unfortunately, insulin and several oral anti-diabetic drugs increase body weight. For example, after one year of treatment, a study showed that patients on thiazolidinedione (TZD) treatment gained 5.0 kg, in comparison with a 3.3 kg weight gain in those using insulin and 1.8 kg in those treated with sulfonylureas (SUs). In contrast, patients on metformin lost 2.4 kg [11]. In the United Kingdom Prospective Diabetes Study, an increase in body weight was associated with intensified treatment and improved glycemic control. The patients on intensive treatment gained 3 kg more than conventionally treated patients during the 10-year follow-up period, with most of the weight gain occurring within the first 12 months. Weight gain was associated with all drugs used for intensive intervention, with the exception of metformin. Weight gain was highest among the insulin-treated patients, who gained a mean of 6.5 kg [12,13].

Weight gain in type 1 diabetes is often perceived as desirable; however, overweight or obesity in type 1 diabetes patients can become a problem with intensive insulin therapy. The Diabetes Control and Complications Trial showed that insulin-associated weight gain was greater in patients receiving intensive treatment compared with that associated with conventional treatment (5.1 vs. 3.7 kg during the first 12 months of therapy), but the mean weight of both groups increased to values beyond ideal. After 12 months of therapy, the intensively treated group had a weight that was 10% above the ideal. After 8 years, body weight continued to increase every year in both groups, more so in the intensively treated cohort. After about 6 years of follow-up, the patients in the intensively treated group gained nearly 5 kg more weight than their conventionally treated counterparts [[14], [15], [16]]. How does chronically elevated insulin or improvement in glycemic control in diabetes result in weight gain? A possible explanation is a defensive or unconscious increase in food intake caused by the fear or experience of hypoglycemia. Insulin significantly increases the risk of hypoglycemia. In fact, some patients increase their intake of carbohydrates episodically or chronically to counteract the threat or experience of hypoglycemia. Increased insulin levels in response to increased caloric intake promote adipogenesis and lipid storage. Weight gain in treated diabetes patients may also result from the resolution of glycosuria. If the food intake is not reduced to compensate for improved glycemic control, the reduction in glycosuria will result in a net gain in weight. Combining sodium glucose co-transporter 2 (SGLT2) inhibitors, which induce glycosuria, with insulin not only improves hyperglycemia but also lessens insulin-associated weight gain [17]. Subcutaneous administration of insulin may also contribute to weight gain in diabetes patients. When insulin is given subcutaneously, the absorbed insulin first circulates systemically, so muscle and adipose tissues are over-insulinized while the liver is under-insulinized. It is possible that systemically elevated insulin levels promote fat

accumulation, which in turn increases therapeutic insulin requirements [16]. Novel long-acting basal insulin analogs have less day-to-day variability of action and thus less weight gain than that associated with traditional insulin [18]. Weight management through diet and exercise is essential for all patients with diabetes. Weight reduction in patients with T2D can decrease diabetes-related complications and improve cardiovascular risk factors. Recent studies have shown a strong relationship between the magnitude of weight loss and the likelihood of diabetes remission [19]. Antihyperglycemic agents have significant effects on body weight. Metformin is the most commonly used first-line therapy for T2D and often induces weight loss or is generally considered weight-neutral (Table 1). Among other anti-diabetic drugs, dipeptidyl peptidase-IV (DPP-IV) inhibitors are weight-neutral. In contrast, insulin, SUs, and TZDs are associated with weight gain. However, SGLT2 inhibitors, amylin analogs, glucagon-like peptide-1 (GLP-1) receptor agonists, and dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor co-agonist promote significant weight loss [20,21]. Thus, adjunctive treatment with metformin, SGLT2 inhibitors, DPP-IV inhibitors, GLP-1 receptor agonists, and GIP/GLP-1 receptor co-agonist should be encouraged to reduce insulin doses and avoid weight gain in patients with T2D. Moreover, practitioners should consider weight-neutral alternatives to medications for hypertension, depression, and other diseases when treating patients with diabetes.

Insulinoma, the most common functioning islet cell tumor of the pancreas, is a rare cause of rapid weight gain. Patients with insulinoma present with symptoms of hypoglycemia secondary to excessive and uncontrolled secretion of insulin. Common symptoms range from intense hunger, tremor, palpitations, and sweating to severe neuroglycopenic manifestations such as anxiety, confusion, behavioral changes, and coma. Symptoms often occur in the morning after an overnight fast and may be precipitated by exercise. The symptoms are episodic due to the intermittent secretion of insulin by insulinoma. Patients with insulinoma learn to avoid these symptoms by eating frequent meals and often high-sugar snacks, which promote weight gain. The diagnosis of insulinoma is established with the determination of fasting hyperinsulinemia (plasma insulin >6 μIU/ml) and symptomatic hypoglycemia (fasting plasma glucose <45 mg/dl). Increased levels of C-peptide and proinsulin distinguish insulinoma from factitious insulin therapy [22]. Several options are available for imaging and localizing insulinoma tumors, including ultrasonography, computed tomography, and intra-arterial calcium stimulation with venous sampling [3]. Surgical resection is the treatment of choice and offers the only chance of curing insulinoma [14,15]. Malignant insulinoma is extremely rare. Aggressive surgical and medical approaches, including administration of octreotide, are recommended in patients with malignant insulinoma to control hypoglycemia. Continuous glucose monitoring can help detect and prevent hypoglycemic episodes and monitor responses to therapy in patients with insulinoma .

Cortisol is the main active GC in humans and an important regulator of many physiological pathways, particularly during stress or illness [28]. GCs are involved in several physiological processes, including metabolism, immune response, growth and development, and reproduction. Secretion of GCs by the adrenal cortex is normally regulated by the hypothalamo-pituitary-adrenal (HPA) axis (Fig. 1). Activation of the HPA axis starts with the secretion of hypothalamic corticotropin-releasing hormone (CRH), stimulation of pituitary pro-opiomelanocortin (POMC) gene transcription, secretion of the POMC-encoded adrenocorticotropic hormone (ACTH), and stimulation of adrenal GC synthesis and secretion (Fig. 2). GCs, in turn, inhibit CRH gene expression and secretion at the hypothalamic level and POMC transcription and ACTH secretion in the anterior pituitary, thereby establishing a regulatory feedback loop [19]. The activity of the HPA axis can further be increased in response to physiological and emotional stress. Once secreted, circulating GCs are bound to and transported by plasma proteins such as corticosteroid-binding globulin and albumin [11]. GCs mediate their physiologic effects by binding to an intracellular receptor, the GC receptor, in the nuclear receptor superfamily of transcription factors. Upon GC binding in the cytosol, the GC receptor translocates into the nucleus, where it serves as a DNA sequence-specific transcriptional regulator of distinct GC-responsive target genes. The main biological functions of GC include the suppression of inflammation and the control of energy homeostasis. Excessive GC from exogenous treatment, e.g., for asthma and inflammatory conditions, or from endogenous overproduction due to pituitary adenoma, ectopic

ACTH-producing tumors, or adrenal tumors, results in central obesity, sarcopenia, hyperglycemia, insulin resistance, dyslipidemia, fatty liver, hypertension, and immunodeficiency (Table 1). Some of these complications of GC excess (Cushing's syndrome) resemble the metabolic syndrome associated with common forms of obesity [12]. Cushing syndrome is a rare condition that results from prolonged exposure to high circulating cortisol levels. Cushing syndrome can be divided into (i) ACTH-dependent Cushing syndrome, in which inappropriately high plasma ACTH concentrations stimulate the adrenal cortex to produce excessive amounts of cortisol, and (ii) ACTH-independent Cushing syndrome, in which excessive production of cortisol by abnormal adrenocortical tissue causes the syndrome and suppresses the secretion of both CRH and ACTH. ACTH-dependent Cushing syndrome accounts for about 80% of cases of endogenous hypercortisolism. Most cases of Cushing syndrome are caused by ACTH-secreting pituitary adenomas, often benign adenomas. The incidence of pituitary-dependent Cushing disease and adrenal adenomas in women is three to four times that of men [3]. The clinical features of Cushing syndrome may vary depending on the extent and duration of excess cortisol exposure. The typical symptoms and signs include a rapid increase in body weight, central obesity, mooning and plethora of the face, dorsocervical fat pad (buffalo hump) and supraclavicular fat pad, oligomenorrhea or amenorrhea, decreased libido in men, spontaneous ecchymoses, proximal muscle wasting and weakness, and the development of multiple wide purplish striae on the abdomen or proximal extremities. Depression and insomnia are common in Cushing syndrome. Patients may have mild hirsutism and acne, but severe androgenization, especially hirsutism and virilization, strongly suggests adrenal carcinoma. Cutaneous hyperpigmentation occurs in patients with ectopic Hypercortisolism in chronic kidney disease seems to be associated with activation of the HPA axis. The dexamethasone-CRH and desmopressin stimulation test has been used to distinguish patients with pseudo-Cushing syndrome from those with Cushing syndrome. The test is performed with low-dose DST followed by CRH (1 μg/kg body weight) stimulation and cortisol measurements. In patients with pseudo-Cushing syndrome, the pituitary corticotroph is appropriately suppressed by GCs and does not respond to CRH, while in Cushing syndrome, the corticotroph tumor is resistant to dexamethasone and responds to CRH. Therefore, a serum cortisol level greater than 1.4 μg/dL in response to CRH after dexamethasone suppression supports the diagnosis of Cushing syndrome, whereas lower cortisol values are seen in normal individuals and those with pseudo-Cushing syndrome. The desmopressin stimulation test is performed in the morning, measuring circulating ACTH and cortisol levels before and after desmopressin (10 μg) administration. Despite many limitations, these tests may provide valuable diagnostic information to distinguish between Cushing syndrome and pseudo-Cushing syndrome. Measurements of late-night salivary or midnight serum cortisol can also be used to differentiate patients with Cushing syndrome from those with pseudo-Cushing syndrome. The circadian rhythm of cortisol is preserved in pseudo-Cushing syndrome but disrupted in Cushing syndrome [43]. While true hypercortisolism will persist and the symptoms will worsen over time in Cushing syndrome, hypercortisolism associated with pseudo-Cushing syndrome typically resolves spontaneously or following definitive treatment, e.g., antidepressant treatment or abstinence from alcohol [6].

Studies in individuals with obesity have demonstrated increased 11β-HSD1 expression and activity in subcutaneous and omental adipose tissue, with positive correlations with body mass index (BMI), body fat, and insulin resistance [18]. However, the role of 11β-HSD1 in individuals with metabolic syndrome and T2D has not been consistent. In a case report of Cushing disease that failed to present with a classical Cushingoid phenotype, a partial functional defect of 11β-HSD1 activity was identified, suggesting that intracellular 11β-HSD1 activity may significantly affect clinical manifestations in Cushing syndrome. Pharmacologic inhibition of 11β-HSD1 may offer a therapeutic strategy for obesity-related metabolic disorders. However, selective 11β-HSD1 inhibitor treatment in obesity, metabolic syndrome, and T2D has shown overall negative results in clinical trials.

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