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Eating Behavior and Body Weight Alterations in Endocrine Disorders: An In-Depth Narrative Review

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Abstract Several excellent studies use the terms feeding behavior (FB) and eating behavior (EB) interchangeably, although they differ in scope. In the present work, FB refers to neuroendocrine regulation, experimental models, and physiological mechanisms, whereas EB pertains to the clinical, psychological, and social aspects observed in humans. FB is shaped by multiple influences—genetic, psychological, and hormonal—within broader socioeconomic, political, cultural, religious, and nutritional contexts. It can therefore be examined from complementary perspectives, particularly neurobiological, clinical, and therapeutic. Body weight (BW) partially reflects FB and its fluctuations over time. This in-depth narrative review explores alterations in EB and BW associated with various endocrine disorders, including hypothalamic syndrome; pituitary cachexia (Simmonds disease); thyroid dysfunction (hyperthyroidism and hypothyroidism); parathyroid diseases; glycemic disturbances (e.g., diabetes mellitus and insulinoma-induced hypoglycemia); disorders of the hypothalamic–pituitary–ovarian axis (e.g., premenstrual syndrome, contraceptive-related changes, and polycystic ovary syndrome); adrenal disorders (Cushing syndrome and adrenal insufficiency); and growth hormone (GH) imbalances (gigantism, acromegaly, and GH deficiency). Whereas many reviews have focused on hormonal alterations underlying obesity as a distinct nosological entity or on primary eating disorders such as anorexia nervosa, bulimia nervosa, and binge eating disorder, the present review specifically addresses changes in EB and BW as secondary manifestations of endocrine dysfunction. These alterations are discussed primarily as clinical signs and symptoms, along with their underlying pathophysiological mechanisms. Relevant historical and therapeutic aspects are also considered.

Keywords: *appetite, craving, disordered eating, hyperphagia, hypophagia, hypothalamic syndrome, obesity*

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1. Introduction

This narrative review provides an in-depth and integrative analysis of how endocrine disorders influence eating behavior (EB) and body weight (BW), aiming to guide readers through both pathophysiological mechanisms and clinical implications.

Hormones are quintessential mediators of intercellular communication, operating through a sophisticated network that encompasses both distant and local signaling mechanisms. The telecrine (distant secretion) component of the traditional endocrine (internal secretion) system coexists with various local secretory modalities—including paracrine and juxtacrine signaling (between adjacent cells), autocrine signaling (affecting the same cell), and intracrine and cryptocrine signaling (acting within the cell itself).

The hypothalamic–anterior pituitary (AP) axis forms an anatomical and functional unit—a neuroendocrine short loop—connected by a neurohemal interface known as the median eminence, a circumventricular organ that typically lacks a blood–brain barrier (BBB). This structure allows neurohormones to flow from the hypothalamus (central nervous system or CNS) to the AP (or adenohypophysis) and subsequently to other peripheral endocrine glands, forming long-loop regulatory circuits (Figure 1).

Briefly, in the hypothalamus, magnocellular (large) neurons project to the posterior pituitary (or neurohypophysis) and secrete two nonapeptides—oxytocin (OT) and vasopressin (also known as antidiuretic hormone, ADH)—whereas parvocellular (small) neurons release peptides that regulate AP hormone secretion [1,2]. Hypothalamic OT-secreting neurons also project to other brain regions involved in the regulation of feeding behavior (FB), including the amygdala, area postrema, nucleus of the solitary tract, and dorsal motor nucleus of the vagus nerve (the tenth of twelve paired cranial nerves) [3]. When administered intracerebrally or intracerebroventricularly, OT reduces food intake (FI) and BW in both wild-type and genetically obese rats [3]. In humans, OT may affect FI and meal preferences, particularly for carbohydrates and sweets [3]. Moreover,

OT appears to preferentially suppress the consumption of sweet-tasting carbohydrates by acting both on the brain's reward circuits and on sweet taste receptors [4]. In addition to regulating the intake of sweet-containing foods, OT also inhibits sodium chloride consumption [5,6].

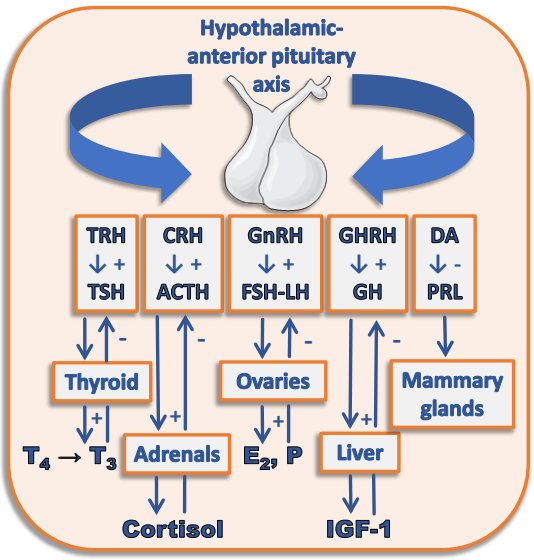
The mesolimbic dopamine (DA) pathway, regulated by DA, plays a key role in motivation and the pleasure associated with feeding; however, homeostatic signals that regulate energy balance can be overridden by emotional responses—particularly those involving the amygdala—leading to increased consumption of high-calorie foods even when a person is not hungry [7].

Hormone production is not limited to traditional endocrine glands; rather, it is widespread, with nearly every tissue in the body capable of producing its own signaling molecules. For example, muscles secrete myokines such as irisin (112 amino acids or AAs), and adipocytes release adipokines such as leptin [8,9,10]. Leptin is a 167-amino-acid adipokine, further discussed in Section 3 [8] [11]. Tumor necrosis factor-alpha (TNF-α), a 157-amino-acid polypeptide, is classified not only as an adipokine but also as a proinflammatory cytokine; it is also addressed in Section 3 [12,13]. The term adipokine refers to a broad class of cytokines and hormones derived from adipose tissue (AT), which are involved in various physiological processes (including vascular renewal) and are dysregulated in conditions such as obesity (OB) and insulin resistance (IR) [12,14].

Gastrointestinal (GI) hormones—such as gastric inhibitory polypeptide (GIP), now also known as glucose-dependent insulinotropic polypeptide, a 42-amino-acid peptide—are essential for nutrient processing and the regulation of glucose metabolism; they may also influence postprandial blood redistribution [15,16,17]. In addition, GI hormones—including GIP, glucagon-like peptide-1 (GLP-1; 30 AAs), and cholecystokinin (CCK; 33 AAs)—play key roles in the regulation of FI [18,19] (see Section 3).

Gastrin, a 17–amino acid peptide hormone secreted by G cells in the stomach and duodenum, is best known for stimulating gastric acid secretion but has also been recognized as a satiety signal in rodents, strongly inhibiting FI in neonatal chicks in a dose-dependent manner for approximately two hours [20,21,22,23]. However, gastrin is not considered a primary satiety hormone in humans: although its potential role in regulating FI has been studied, circulating gastrin concentrations in OB and after bariatric surgery remain unclear [24]. Gastrin-releasing peptide (GRP), a 27–amino acid peptide, stimulates gastrin release but can also inhibit it indirectly via somatostatin, a 14–amino acid peptide; GRP itself exerts anorexigenic effects in both mammalian and avian species [25,26,27,28].

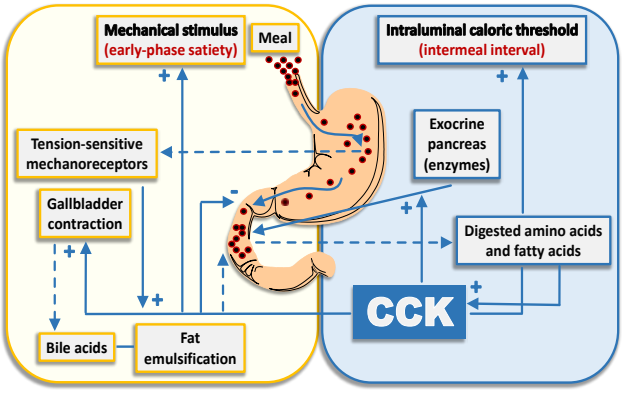
As food is swallowed, gastric distension occurs, triggering the release of CCK, expressed in the hypothalamus, which contributes to the early phase of satiety by promoting meal termination [19,29,30,31]. CCK also appears to regulate the intermeal interval by slowing gastric emptying and acting as a peripheral satiety signal in response to intestinal caloric content [30]. In addition, CCK induces gallbladder contraction and stimulates pancreatic exocrine secretion [32] (Figure 2).



+: positive feedback; -: negative feedback; **TRH**: thyrotropin-releasing hormone; **CRH**: corticotropin-releasing hormone; **GnRH**: gonadotropin-releasing hormone; **GHRH:** growth hormone-releasing hormone; **DA**: dopamine (prolactin-inhibiting hormone); **TSH**: thyroid-stimulating hormone; **ACTH**: adrenocorticotropic hormone; **FSH**: follicle-stimulating hormone; **LH**: luteinizing hormone; **GH**: growth hormone; **PRL**: prolactin; **T_4**: tetraiodothyronine or thyroxine (prohormone); **T_3**: triiodothyronine (active hormone); **E_2**: estradiol; **P**: progesterone; **IGF-1**: insulin-like growth factor 1.

Note. Endocrine glands release their secretions directly into the bloodstream, whereas exocrine glands discharge them through ducts. PRL is among the essential regulators universally required for lactation—encompassing milk synthesis and release—although this process is under complex, multihormonal control [2]. The neurohypophysis (posterior pituitary) does not synthesize hormones; rather, it serves as a storage and release site for two specific hormones—oxytocin and ADH—into the bloodstream.

Figure 1. Diagram of the traditional hypothalamic–anterior pituitary axis and its interactions with peripheral endocrine and exocrine (mammary) glands



Adapted from [19,29,30,31].

+: stimulatory effects; -: inhibitory effects; **dotted arrows** represent fewer, intermediate mechanisms; **bold arrows** indicate the numerous biological effects of CCK.

Note. CCK secretion is most potently stimulated by triglyceride hydrolysis products and by the essential amino acids tryptophan and phenylalanine, whereas carbohydrates are less potent [33].

Figure 2. Diagram of the mechanisms regulating secretion and effects of CCK

The neuroendocrine system is considered traditional not only because it has been studied for a longer time, but also because it has played a central role in elucidating the functions of major regulatory axes, such as the hypothalamic-pituitary-thyroid and hypothalamic-pituitary-adrenal systems (Figure 1). By contrast, the secretion of certain hormones—such as insulin (51 AAs) and parathyroid hormone (PTH; an 84-amino-acid polypeptide)—is tightly regulated by nutrient or ion concentrations, such as glucose and calcium, respectively [34]. A distinct hypothalamus-to-β cell circuit further modulates insulin secretion (see Section 8 and Figure 5) [35,36,37].

Metabolism refers to the set of biochemical transformations undergone by all substances in living organisms. It includes two fundamental processes: anabolism, the synthesis of complex molecules, and catabolism, their breakdown. Intermediary metabolism describes these transformations in greater detail, particularly the chemical pathways involved in the production, storage, and utilization of energy. Within this framework, hormones can be broadly classified as anabolic—such as insulin and growth hormone (GH; see Section 11)—or catabolic, such as triiodothyronine (T_3) and cortisol, both of which exert significant effects on muscle tissue. Consequently, proximal myopathy may occur in conditions characterized by excessive catabolic hormone activity, such as thyrotoxicosis (Section 6 and Subsection 6.1) and Cushing syndrome (CS) (Subsection 10.1) [38,39,40].

Understanding the metabolic effects of hormones enhances the comprehension of the pathophysiology underlying feeding and weight disorders in endocrine diseases. For instance, cortisol receptors are present in most cells of the body, and a well-established relationship exists between elevated cortisol levels and increased adiposity [41]. This partially explains the characteristic moon face and central obesity (COB) observed in CS. Moreover, cortisol exerts catabolic effects on proteins, impairing collagen production and protein synthesis. These actions contribute not only to the above-mentioned myopathy but also to skin thinning with striae and delayed wound healing.

Neuroendocrinology—the study of interactions between the nervous and endocrine systems—and neurobiology—the study of nervous system function—are deeply intertwined. Remarkable advances in this interdisciplinary field continue to reveal their convergence, particularly in the regulation of FB and BW.

In this review, particular attention is given to the pre-ingestive, ingestive, and post-ingestive components of normal EB—namely hunger, appetite, satiation, and satiety (see Section 3)—as well as to their alterations, including hyperphagia (or polyphagia), hypophagia, anorexia, pica, food cravings, and disorders of the satiation process (e.g., diabetic gastroparesis). Changes in BW, such as COB and cachexia, are also addressed. Notably, cachexia may occur in untreated thyrotoxic patients and individuals with diabetic neuropathy.

Several excellent studies in the specialized literature use the terms and abbreviations for (FB) and (EB) interchangeably; however, these terms have distinct scopes. In the present work, FB refers to neuroendocrine regulation**,** experimental models, or physiological mechanisms (e.g., hypothalamic regulation, leptin signaling), whereas EB pertains to the clinical, psychological, or social aspects in humans (e.g., appetite changes in type 2 diabetes mellitus (T2DM), binge eating, patient-reported habits).

Feeding peptides—including peripheral peptide hormones and central neuropeptides—are critical components of the complex signaling network that the CNS orchestrates to regulate energy homeostasis [42]. As noted in this introduction, the author carefully specified the number of amino-acid residues in each molecule discussed. Molecular size is an important physicochemical characteristic: molecules with fewer than 50 amino-acid residues are generally classified as peptides, whereas longer chains are termed polypeptides; the precise cutoff varies among sources [43]. In fact, all of the peptides introduced above—except irisin, leptin, TNF-α, insulin, and PTH, which are polypeptides—contain fewer than 50 amino-acid residues. By contrast, steroid hormones are low–molecular–weight compounds, including those that regulate FB, such as estrogens (Es) and progesterone (P) (discussed further in Section 9) and cortisol (Section 10).

In addition to the list of abbreviations, frequently recurring terms in this work are presented in full upon first mention, with their corresponding abbreviations used thereafter. Moreover, the term disordered eating (DE) refers to abnormal eating behaviors secondary to endocrine or metabolic disturbances, thereby distinguishing them from primary psychiatric eating disorders, as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) and the *International Classification of Diseases*, 11th Revision (ICD-11) [44,45].

For clarity and didactic synthesis, each disorder section and subsection concludes with a concise **Eating Behavior Profile** highlighting the principal behavioral alterations. A comparison between alterations in EB and BW is presented in Figure 7 at the end of the work.

Table 1 summarizes the definitions of the signs and symptoms related to the eating and weight disorders addressed in this review.

Table 1. Eating and Weight Disorders Addressed in This Review

Signs and symptoms	Definitions	Refs.
Hyperphagia (or polyphagia)	Excessive food intake	[2,46]
Hypophagia	Reduced food intake	[47]
Aphagia	Refusal of food, or inability to eat	[2]
Anorexia	↓ or loss of appetite	[48]
Binge eating	Consumption of unusually large quantities of food in a discrete period, accompanied by a sense of loss of control and without the regular use of compensatory behaviors such as self-induced vomiting	[49]
Pica	Compulsive eating of non-nutritive, non-food substances, such as ice (pagophagia),	[50]

Signs and symptoms	Definitions	Refs.
	dirt (geophagia), gravel, flaking paint or plaster, clay, hair (trichophagia), or laundry starch (amylophagia)	
Food craving	Intense desire or longing for a particular substance	[51]
Sweet craving	Strong desire or yearning to consume sweet foods and beverages	[52]
Salt craving	Strong drive to ingest sodium chloride	[2]
Early satiation	Sensation of stomach fullness shortly after beginning a meal, which is disproportionate to the amount of food consumed and leads to an inability to finish the meal	[53]
Nausea	Unpleasant sensation, typically localized to the throat or epigastric area, that signals an impending urge to vomit	[54]
Vomiting	Forceful expulsion of gastric contents through the mouth, typically involving involuntary contractions of the abdominal and diaphragmatic muscles	[54]
Food aversion	Feeling of extreme repugnance accompanied by avoidance or rejection of food	[55]
Central obesity	A hallmark of metabolic syndrome, is characterized by excessive abdominal adipose tissue—typically defined by a waist circumference of ≥ 94 cm in men and ≥ 80 cm in women—often accompanied by systemic inflammation	[56,57]
Sarcopenic obesity	Coexistence of sarcopenia and obesity (see Subsection 10.1)	[58,59]
Cachexia	Simultaneous loss of muscle and fat mass	[60]

Refs: references; ↓: decrease **≥:** greater than or equal to.

2. Methodology

The present topic, in addition to being relatively underexplored, is fragmented across the specialized literature. To assemble the pertinent evidence, systematic searches were conducted using predefined keywords in academic search engines (e.g., Google Scholar) and bibliographic databases, including MEDLINE, PubMed, Scopus, Embase, the Cochrane Library, and CINAHL, primarily covering the period from January 2020 to December 2025. Earlier publications of historical relevance were examined irrespective of their year of publication. Articles published in English, French, Spanish, and Portuguese were considered. Eligible sources included peer-reviewed original research articles, narrative and systematic reviews, clinical guidelines, and landmark experimental studies involving human and/or animal models. Case reports, regarded as a foundational component of medical research in the study of rare diseases, were also included as eligible sources. Studies were selected based on their relevance to the topic, methodological rigor, and conceptual contribution to advancing current understanding of the underlying mechanisms. Authoritative textbooks were consulted for foundational and widely accepted concepts, and monographs were reviewed for their specialized and in-depth treatment of specific subtopics.

The review is organized to promote conceptual clarity. An initial integrative overview of FB and BW regulation establishes the physiological foundation, followed by sections dedicated to the traditional neuroendocrine regulatory axes and the consequences of their dysregulation. Each disorder section and subsection concludes with a concise **Eating Behavior Profile** summarizing the principal behavioral alterations. A final synthesis comparing alterations in EB and BW is presented in Figure 7.

3. Feeding Behavior and Body Weight Regulation: An Integrative Overview

FB and BW are intrinsically interconnected in sustaining life. FB determines energy intake and thus directly influences BW, whereas energy stores—reflected in body mass—reciprocally modulate subsequent feeding. In mammals, AT serves as the principal energy reservoir, storing fat in the form of neutral triacylglycerols (or triglycerides) [61]. These energy reserves act as metabolic signals that regulate the drive to eat.

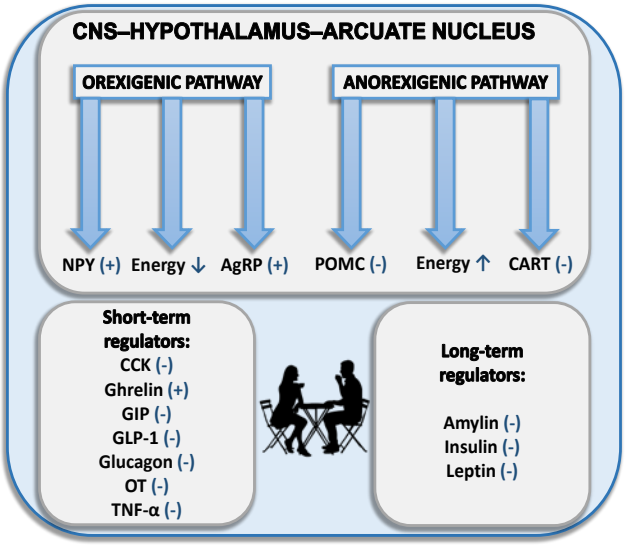
For example, hypothalamic neurons can sense key circulating energy substrates, such as glucose (4 kcal/g) and free fatty acids (9 kcal/g), and initiate essential metabolic responses, including the regulation of FI, metabolic rate or energy expenditure (EE), and glucose homeostasis [62,63]. Leptin, a hormone produced by white AT, crosses the BBB via tanycytes in a leptin-receptor-dependent manner and signals satiety to the hypothalamus, reducing appetite and FI [64,65,66,67]. Rodent models of OB, such as the Zucker fa/fa rat, demonstrate how altered FBs (e.g., hyperphagia) and hormonal changes (including hyperinsulinemia and increased opioid activity) contribute to weight gain (WG) [68]. This reciprocal interaction between FB and BW exemplifies the homeostatic regulation of energy balance, allowing the body to maintain metabolic stability.

The concepts of constancy of the internal environment and homeostasis were introduced by Claude Bernard (1813–1878) and Walter B. Cannon (1871–1945), respectively, to explain the stability essential for the survival of living systems [69,70,71].

Although the hypothalamus is considered tertiary in the hierarchical organization of neuroendocrine regulation (Figure 1)—following the AP (secondary) and the peripheral endocrine glands (primary)—it nevertheless plays a central role in the neurobiological control of FB. Indeed, hypothalamic lesions—such as those produced by tumor processes—can lead to profound disturbances in FB and BW. For example, damage to the dorsolateral nucleus (the feeding center) may result in aphagia, starvation (or food deprivation), progressive weight loss (WL), cachexia, and ultimately death, whereas injury to the ventromedial nucleus (the satiety center) typically produces hyperphagia and OB, as discussed in Section 4 [72,73,74,75,76].

The central neural pathways involved in the homeostatic regulation of FI originate primarily in the arcuate nucleus of the hypothalamus and comprise two key, opposing mechanisms that influence both FI and EE

[77]. The first is the orexigenic pathway, which secretes neuropeptide Y (NPY)—a 36-amino-acid peptide—and agouti-related peptide (AgRP), a 132-amino-acid polypeptide, whose activation stimulates FI while reducing EE [77,78]. The second is the anorexigenic pathway, which secretes proopiomelanocortin (POMC)—a predominantly pituitary polyprotein that yields multiple active hormones—and cocaine- and amphetamine-regulated transcript (CART), two polypeptides of 129 and 116 AAs generated by alternative splicing, whose activation suppresses FI while increasing EE [77,79,80,81]. Short- and long-term regulators of FI are schematically represented in Figure 3 [77].



CNS: central nervous system; **thick arrows**: indicate the flow of the main pathways; +: stimulates food intake; -: inhibits food intake; ↓: decreases energy; ↑: increases energy; **NPY**: neuropeptide Y; **AgRP**: agouti-related peptide; **POMC**: proopiomelanocortin; **CART**: cocaine- and amphetamine-regulated transcript; **CCK**: cholecystokinin; **GIP**: glucose-dependent insulinotropic polypeptide; **GLP-1**: glucagon-like peptide-1; **OT**: oxytocin; **TNF-α:** tumor necrosis factor-alpha.

Figure 3. Simplified diagram of the neurobiological regulation of feeding behavior Adapted from [77]

In many contexts, compounds involved in the regulation of FB act either as stimulants—such as corticotropin-releasing hormone (CRH) via cortisol (see Section 10), sauvagine (40 AAs), peptide YY (36 AAs), pancreatic polypeptide (36 AAs), β-endorphin (31 AAs), and dynorphin (17 AAs)—which often promote FI, or as inhibitors—such as CRH, central insulin, vasoactive intestinal polypeptide (28 AAs), bombesin (14 AAs), neurotensin (13 AAs), and cerulenin (a 12-carbon fatty acid amide)—that generally suppress it [82,83,84,85] [86,87,88,89] [90,91,92,93] [94,95,96].

Ordinarily, β-endorphin levels rise in response to acute stress due to activation of the hypothalamic–pituitary–adrenal (HPA) axis, and this response occurs rapidly after the onset of the stressor [97]. This opioid hormone is released from the POMC precursor [92,96,98,99]. The mechanism by which β-endorphin stimulates FI is not yet fully understood, but it is believed to involve self-regulation of POMC neurons through negative feedback [100].

Fatty acid synthase is a multifunctional enzyme system that catalyzes the formation of fatty acids from acetyl-CoA, malonyl-CoA, and nicotinamide adenine dinucleotide phosphate, playing a central role in lipid biosynthesis [101]. The naturally occurring inhibitor of this enzyme, cerulenin, together with its more potent synthetic analog C75, has been reported to reduce BW, suppress FI, and increase EE when administered to mice—possibly by acting on hypothalamic glucose-sensing neurons through a leptin-independent mechanism involving malonyl-CoA accumulation [101,102].

Sauvagine, a peptide isolated from the skin of the South American frog *Phyllomedusa sauvagei* and structurally related to fish urotensin I and mammalian CRH, inhibits feeding when injected intracerebroventricularly into rats deprived of food for 18 hours [93,103].

Regarding non-homeostatic processes, components such as emotion, reward, memory, perception, and cognitive control systems each contribute significantly to the regulation of FB [7]. For example, memory processes are essential for food-related decision-making, involving the storage of associations between foods and their outcomes that underlie conditioning, while working memory—responsible for maintaining and manipulating information—is critical for integrating goal values; recent research has investigated its role in EBs [104]. Cognitive satiety, often termed sensory-specific satiety, has been observed in various contexts involving specific tastes, aromas, and textures [105].

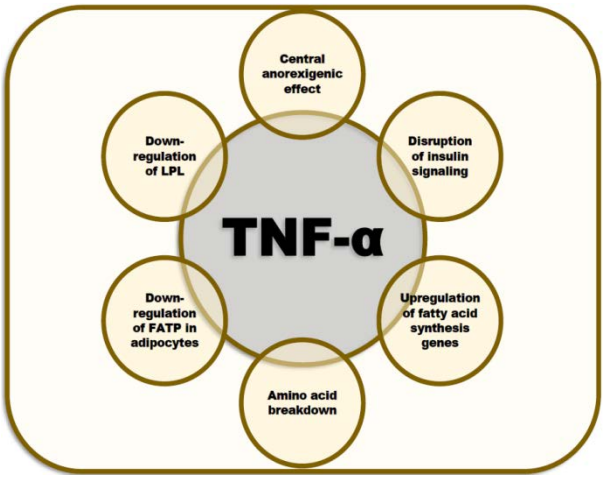
Furthermore, the complexity increases when the microbiota–gut–brain axis is added to the discussion. In fact, the neuroendocrine system constitutes a major bidirectional pathway within this axis, being both influenced by food choices and serving as a key site for host–microbe crosstalk [106]. Microbial endocrinology—the study of neuroendocrine host–microbe interkingdom communication—is still in its early stages but provides an important, though not exclusive, lens through which diet, nutrition, and the microbiota–gut–brain axis may be mechanistically linked [106].

At this point, it is worth emphasizing the theoretical and clinical relevance of TNF-α in the pathophysiology of feeding and weight disorders. First identified in 1975 by Carswell et al. as a serum factor capable of inducing hemorrhagic necrosis in tumors, TNF-α was later found to be identical to cachexin, a mediator of infection-associated wasting [107,108]. It quickly attracted attention for its pleiotropic nature, occupying a central position at the intersection of immunology—as a proinflammatory cytokine and chemokine—endocrinology, and oncology, where it functions as an adipokine [109,110,111,112,113]. Clinically, its levels are elevated at both extremes of BW—cachexia and OB—leading to its original dual designation, TNF-α/cachexin [114,115,116,117,118] (Figure 4).

In simplified terms, TNF-α from multiple sources (e.g., immune cells, microglia, and adipocytes) exerts anorexigenic effects in the arcuate nucleus of the hypothalamus by inducing production of alpha-melanocyte-stimulating hormone and CART in POMC-expressing neurons and by decreasing production of the orexigenic peptides AgRP and NPY in AgRP neurons via modulation of intracellular AMP-activated protein kinase, which is itself influenced by hormones and energy substrates and integrates orexigenic and anorexigenic signals within the arcuate nucleus [119]. In OB, TNF-α is chronically elevated in AT, promoting IR and

hyperinsulinemia, and increasing transforming growth factor-β, which is linked to myocardial diseases [117,120,121].

In short, EB unfolds as a periodic sequence of events. First is the pre-ingestive phase, characterized by arousal—a nonspecific sensation of hunger, often described as gnawing or rumbling in the stomach, or as a feeling of emptiness and corresponding to the question, "Is there anything to eat?". During this phase, the individual is oriented toward searching for, selecting, acquiring, storing, and preparing food. Next, the ingestive phase, guided by appetite, corresponds to the question, "What do I want to eat?"—a specific internal signal (Figure 3) that initiates eating and, through satiation—the dynamic component of satiety—leads to satiety. Finally, the post-ingestive phase is marked by well-being and drowsiness, which define satiety and terminate FI. Experimental evidence indicates that this drowsiness is related to the secretion of CCK (Figure 2) [82,134,135,136,137,138,139,140].



LPL: lipoprotein lipase; **FATP**: fatty acid transport protein.

Note. Complementing **Figure 4**, the acute (short-term) actions of TNF-α within the hypothalamus lead to anorexia, enhanced thermogenesis, and an increased respiratory rate [125]. In lipid metabolism, the multifunctional nature of TNF-α allows it to exert opposing effects: it promotes catabolism through adipocyte lipolysis, thereby favoring EE, and anabolism through lipogenesis in the liver and sebocytes, thereby promoting energy storage—this dual role helping explain its pathophysiological relevance at both extremes of BW, cachexia and OB [126,127,128,129,130,131,132,133].

Figure 4. Diagram of TNF-α effects on feeding behavior and metabolism Adapted from [111,122,123,124]

An illustrative, hypothetical example of the phases of EB—provided here solely to reinforce understanding—is as follows. Someone asks, "Is there anything to eat?". This reflects the pre-ingestive phase, in which a nonspecific hunger signal (arousal) triggers the search for food. On a bright summer day, upon opening the refrigerator, the person notices a sweating jar of lemon juice and decides to drink it. This decision represents the ingestive phase, guided by a specific internal signal, or appetite, that initiates eating. Choosing a cold juice on a hot day also exemplifies alliesthesia—the modulation of food-related pleasure according to the body's internal state—because the cold drink provides cooling relief [141]. This phenomenon, whereby a stimulus may feel pleasant (positive alliesthesia) or unpleasant (negative alliesthesia) depending on its physiological relevance, is experimentally demonstrable (e.g., facial expressions and food-hoarding behavior) and relevant to thermal, gustatory, and olfactory sensations, as well as to BW regulation [142,143]. Finally, after drinking the juice, the person feels satisfied and relaxed, marking the post-ingestive phase, in which satiety and drowsiness signal the end of eating.

4. Hypothalamic Syndrome

The hypothalamus lies beneath the thalamus and is separated from it by the hypothalamic sulcus [144]. Across species, it is typically partitioned into three longitudinal zones (periventricular, medial, and lateral), each comprising four rostrocaudal regions—preoptic, anterior (supraoptic), tuberal, and mammillary [145].

From 1942 onwards, as noted by Kandel et al. [1], lesion and stimulation studies suggested that the lateral hypothalamus functioned as a feeding center and the medial hypothalamus as a satiety center, since damage or activation of these regions produced opposing effects on FI. However, this model proved overly simplistic, as feeding is regulated by distributed neural circuits rather than discrete centers (see Section 3). The effects of hypothalamic lesions are now understood to arise partly from secondary dysfunctions, including altered sensory processing, disruption of metabolic set points, and impaired behavioral arousal due to damage of dopaminergic pathways.

Hypothalamic syndrome (HS) is a rare disorder resulting from disease- or treatment-related injury to the hypothalamus, most commonly associated with noncancerous parasellar masses—such as craniopharyngiomas, germ cell tumors, gliomas, Rathke's pouch cysts, and Langerhans cell histiocytosis—as well as with genetic neurodevelopmental syndromes, including Prader–Willi syndrome (PWS) and septo-optic dysplasia [146].

HS is characterized by intractable WG and severe morbid OB, accompanied by multiple endocrine abnormalities, cognitive impairments such as memory deficits and attention problems, reduced impulse control, and an increased risk of cardiovascular and metabolic disorders [146,147].

PWS warrants particular attention because of its profound impact on FB and BW. First described in 1956, it represents the most common genetic cause of life-threatening OB in humans [148]. Characteristically, FB changes dramatically, with an insatiable appetite emerging between 18 months and 2 years of age [148]. PWS is also considered a model for understanding the ghrelin system, as it constitutes a unique pathological state marked by severe OB and persistently elevated circulating ghrelin levels across all ages. An early switch in ghrelin dynamics may explain the nutritional phases of the disease—from initial anorexia and failure to thrive to subsequent excessive WG, OB, and hyperphagia [149].

Children with PWS also exhibit characteristic food-related behaviors. In a study of 14 affected children, Holm et al. [150] reported that sneaking food was the most common and serious problem, followed by gorging (observed in half of the children) and the consumption of items typically regarded as unappealing or inedible (e.g.,

dog and cat food, berries from ornamental bushes). Many other examples of pica in PWS are documented in the specialized literature [151,152,153].

Families of the 14 affected children mentioned above also reported additional behaviors, including preoccupation with refrigerators and freezers, persistent worries about food availability, and heightened concern with eating [150].

Hyperphagia, driven in part by elevated ghrelin levels, is the most life-limiting symptom in PWS and underscores the urgent need for new pharmacologic therapies [154].

Eating Behavior Profile: Prader–Willi syndrome as prototype; early anorexia; hyperphagic transition around 18 months of age; food-seeking behaviors (sneaking food, gorging, pica, and preoccupation with food storage).

5. Pituitary Cachexia: A Brief Historical Note on Severe Hypopituitarism

In 1914, Morris Simmonds (1855–1925) published the first detailed clinical description of pituitary cachexia [69,70,155]. His account is regarded as the earliest clinical report of anterior pituitary atrophy in humans; in his index patient, the condition was associated with puerperal sepsis and infarction of the anterior lobe [70]. The eponym Simmonds disease was introduced in 1922 by L. Lichtwitz [70,156]. As of August 22, 2025, a Google Scholar search retrieved approximately 2,080 results for Simmonds disease and 135 for Simmonds cachexia.

As stated by Uwaifo [157], pituitary cachexia (Simmonds disease) is a syndrome with diverse etiologies that converge on adenohypophyseal failure accompanied by profound wasting. Reported causes include macroadenomas, traumatic injury, infections, and inflammatory diseases—most commonly tuberculosis and syphilis—among others. Improvements in general nutritional status, earlier recognition of underlying disorders, and the widespread availability of multihormone replacement therapy likely account for the declining prevalence, reduced severity, and fewer contemporary reports of Simmonds disease.

Eating Behavior Profile: anorexia; early satiety; decreased food intake in the context of wasting.

6. Thyroid Dysfunction

The hypothalamic–pituitary–thyroid (HPT) axis is schematically illustrated in Figure 1. Thyroid hormones (THs) play a crucial role in human health. The primary hormone secreted by the thyroid gland is tetraiodothyronine or L-thyroxine (T_4), which acts as a prohormone for triiodothyronine (T_3)—the biologically active form. T_3 exerts widespread physiological effects via high-affinity intranuclear receptors [158]. T_4 is converted into T_3 through monodeiodination, a process mediated by three enzymes collectively known as deiodinases, which regulate the local availability of T_3 in target tissues [159].

Euthyroidism refers to a state of normal thyroid function, in which TH levels remain within the physiological range and support appropriate metabolic and physiological regulation [160].

From an etiologic standpoint, thyrotoxicosis with hyperthyroidism denotes a clinical–biochemical syndrome caused by increased synthesis and secretion of THs by the thyroid gland (e.g., Graves disease, toxic adenoma) [161]. In contrast, thyrotoxicosis without hyperthyroidism refers to elevated THs levels regardless of source, including nonthyroidal origins (e.g., exogenous hormone ingestion, ectopic thyroid hormone production) [161].

The most common cause of hyperthyroidism is Graves disease, an autoimmune disorder first described in 1835 by Robert James Graves (1796–1853), following earlier posthumous observations by Caleb Hillier Parry (1755–1822), and subsequently described by Karl Adolph von Basedow (1799–1854) in 1840 [69,70,162,163]. Its global prevalence is estimated at approximately 2% in women and 0.5% in men [163].

Primary hypothyroidism results from intrinsic thyroid dysfunction leading to impaired hormone synthesis [164]. Chronic autoimmune thyroiditis—first described in 1912 by Hakaru Hashimoto (1881–1934) in Germany—remains the most common cause of hypothyroidism in iodine-sufficient regions worldwide [164,165,166].

Given their broad range of action, THs influence nearly every major physiological system. Consequently, thyroid dysfunction—whether hyperthyroidism or hypothyroidism—can present with a diverse array of signs and symptoms. However, the symptom profile typically reflects either hormone excess or deficiency. For instance, hyperthyroidism is often associated with tachycardia, hyperphagia, WL, and moist skin, while hypothyroidism commonly presents with bradycardia, anorexia, hypophagia, WG, and dry skin. Although the presentation is clearly polarized, these manifestations are sometimes nonspecific and may be misattributed to other medical or psychiatric conditions [167].

Heat intolerance in hyperthyroidism reflects an increase in basal metabolic activity, with enhanced substrate turnover and greater cellular heat production driven by elevated consumption of adenosine triphosphate and oxygen [168]. As a result, patients tend to eat more yet still lose fat stores and muscle mass (Subsection 6.1) [168]. By contrast, hypothyroidism reduces oxygen consumption and carbon dioxide production, leading to a lower EE, diminished substrate catabolism, and often a depressed appetite, as further discussed in Subsection 6.2 [169].

6.1. Hyperthyroidism

In hyperthyroidism, rapid WL—ranging from 3 to 20 kg within a few weeks—is common and may occur despite normal or even increased appetite, sometimes approaching true polyphagia [170]. This heightened food intake may result from the direct actions of THs on central appetite-regulating circuits [171]. Two solute carrier transporters—monocarboxylate transporter 8 and organic anion-transporting polypeptide 1C1—facilitate TH passage across the BBB and into the CNS [172,173]. Notably, T_3 directly stimulates FI at the hypothalamic level, and in rodent models, both peripheral and central hypothalamic administration of T_3 have been shown to increase FI [171,174,175]. The nutritional status in

affected individuals varies according to age, baseline BW, and the extent to which dietary intake compensates for the elevated EE [170].

According to Daher et al., up to 25% of patients with hyperthyroidism may experience mild to moderate diarrhea with frequent bowel movements [176]. Some degree of fat malabsorption is common and may reach up to 35 g/day. In thyrotoxicosis, intestinal hypermotility shortens small bowel transit time—particularly in the presence of diarrhea—and the combination of increased appetite and a high intake of fat-rich foods may contribute to excessive fecal fat loss. Several additional pathophysiological mechanisms may also be involved, including a hypersecretory state of the intestinal mucosa. The adrenergic system appears to play a role, as suggested by improvement in intestinal transit following treatment with the β-adrenergic antagonist propranolol. Furthermore, reduced mixing of food with digestive secretions may impair fat absorption. In addition to propranolol, reducing dietary fat intake can help lessen the frequency of these manifestations (personal unpublished data).

Eating Behavior Profile: normal or, more frequently, increased appetite—sometimes approaching true polyphagia; mild to moderate diarrhea, particularly after fat-rich meals.

6.2. Hypothyroidism

As previously mentioned, hypothyroidism can cause hypophagia—reduced FI—despite an overall tendency toward WG. In rodents, central administration of TRH (a tripeptide) and TSH (a glycoprotein of approximately 28 kDa) reduces FI, with peripheral administration of TRH producing similar effects [171,177]. Experimental hypothyroidism also induces a negative energy balance, accompanied by decreased NPY and increased POMC protein levels in the arcuate nucleus, resulting in a predominance of anorexigenic pathways despite central leptin resistance and nuclei-specific impairment of the leptin signaling cascade [178].

Endocrine disorders are commonly investigated as potential causes of OB but are seldom identified, with thyroid dysfunction often being blamed—particularly in adolescents—although hypothyroidism only rarely leads to significant WG, and treatment of thyroid deficiency seldom results in substantial WL [179]. In fact, WG in hypothyroidism is generally modest and may even be absent in some patients [180]. When present, it primarily reflects water retention rather than fat accumulation. This retention results from reduced T_3 levels, which normally inhibit the production of hyaluronic acid by fibroblasts—a hydrophilic glycosaminoglycan of approximately 8 kDa that contributes to tissue edema [2,180,181].

Hypothyroidism can also impair GI motility and may contribute to the development or exacerbation of gastroparesis [182]. Reduced TH levels decrease overall metabolic activity, including the mechanisms regulating GI motility, which can result in delayed gastric emptying and symptoms of gastroparesis such as early satiety [182].

Eating Behavior Profile: hypophagia; early satiety in the context of delayed gastric emptying (gastroparesis).

6.3. Neurobiological Changes Affecting Food Intake during Thyroid Dysfunction

Thyroid function is modulated by several neurotransmitters, including catecholamines (which exert sympathetic stimulatory effects), acetylcholine (which mediates parasympathetic inhibitory effects via muscarinic receptors), and various neuropeptides such as NPY and calcitonin gene–related peptide [183,184]. In animal models, chronic peripheral administration of 5-hydroxytryptamine or serotonin has been shown to inhibit TH production by reducing 5'-monodeiodinase activity in tissues such as brown AT, thereby decreasing the local conversion of T_4 to the active T_3 and consequently diminishing EE through reduced thermogenesis [184,185]. Serotonin also exerts an anorexigenic effect by suppressing FI [186].

Conversely, THs can modulate neurotransmitter systems. They may increase dopamine catabolism or alter dopamine receptor sensitivity, potentially contributing to symptoms in individuals predisposed to Parkinson disease (PD) [187]. In PD, some patients display food cravings and/or compulsive eating, which can lead to substantial, undesired WG [188].

Ghrelin, a 28–amino acid peptide predominantly secreted by the stomach, is a potent orexigenic (appetite-stimulating) hormone [189]. A recent meta-analysis of 23 studies reported that circulating ghrelin levels are significantly lower in patients with hyperthyroidism than in healthy controls, increasing markedly following treatment [190]. In hypothyroidism, ghrelin concentrations tend to be slightly elevated, although the difference is not statistically significant [190]. These findings, however, do not fully explain the paradoxical clinical manifestations of hyperphagia with WL in hyperthyroidism and anorexia with WG in hypothyroidism.

As previously noted, leptin, secreted by white adipocytes, exerts anorexigenic (appetite-suppressing) effects, whereas NPY, a peptide frequently co-localized with catecholamines in many neurons, stimulates appetite [11,191,192]. Reported elevations of both leptin and NPY in hyperthyroid and hypothyroid states highlight the complex—and sometimes counterintuitive—interactions between THs and neuroendocrine regulators of appetite [193]. More recent data regarding leptin are consistent with this pattern: compared with euthyroid individuals, circulating leptin levels were significantly higher in hypothyroidism and not significantly altered in hyperthyroidism [194].

Overall, thyroid dysfunction disrupts multiple neurobiological pathways that regulate appetite and metabolism, producing paradoxical alterations in both orexigenic and anorexigenic signaling in hyperthyroid and hypothyroid states. These complex and sometimes contradictory patterns highlight persistent gaps in the understanding of the neuroendocrine effects of THs. Bridging these gaps could lead to more accurate diagnostic markers and more targeted therapeutic approaches for metabolic and eating disturbances associated with thyroid disorders.

7. Parathyroid Disorders

The parathyroid glands (typically four small glands located posterior to the thyroid) secrete PTH. This polypeptide hormone is the principal regulator of serum calcium and acts on bone, kidney, and intestine to maintain calcium–phosphate homeostasis [195,196].

7.1. Primary Hyperparathyroidism

Primary hyperparathyroidism (PHPT)—characterized by excessive PTH secretion leading to hypercalcemia—is associated with complex eating- and weight-related disturbances that may present in opposite ways: some patients lose appetite and weight, while others show increased adiposity.

Although appetite changes are not always prominent, hypercalcemia can cause GI symptoms such as nausea, constipation, vomiting, and reduced appetite [197,198]. These manifestations can reduce FI and lead to unintentional WL and nutrient deficiencies, which may require targeted dietary interventions [199].

Conversely, numerous studies report a higher prevalence of OB among patients with PHPT, suggesting a significant association between the two conditions even though causality remains unclear [200,201]. Proposed mechanisms include resistance to PTH in target tissues, adipokine resistance, and reduced lipolysis; some reports also link higher serum PTH and larger parathyroid glands to greater body mass index (BMI) in PHPT patients [200,202,203]. In addition, elevated PTH correlates with higher serum leptin levels, and leptin may stimulate PTH secretion by inhibiting the calcium sensing receptor (CaSR) on parathyroid cells, suggesting potential bidirectional endocrine cross-talk [201,204]. Furthermore, PHPT markedly influences gene regulation in AT, potentially leading to impaired adipocyte function and the release of pathogenic factors that contribute to increased cardiovascular risk [205].

Eating Behavior Profile: nausea; vomiting; constipation; reduced appetite.

7.2. Secondary Hyperparathyroidism

Secondary hyperparathyroidism (SHPT), most commonly associated with chronic kidney disease (CKD), is characterized by compensatory elevations of PTH in response to hypocalcemia and vitamin D deficiency. Patients frequently experience anorexia related to uremia, altered taste perception, and reduced caloric intake driven by metabolic disturbances [206,207].

In advanced stages, particularly among patients receiving dialysis, SHPT is associated with DE patterns—notably protein-energy wasting, avoidance of phosphate-rich foods, and poor adherence to complex dietary regimens [208]. Diminished appetite has been reported in 40–50% of dialysis patients [208]. The combined burden of dietary restrictions together with olfactory and gustatory disturbances contributes to food aversion (see Table 1 for definition) and reduced appetite in CKD, ultimately lowering quality of life and amplifying the impact of parathyroid dysfunction on EB [208,209,210].

For the reasons discussed above, WL is recognized as one of the major adverse outcomes of SHPT [211,212,213]. By contrast, higher BMI—particularly in the OB range—has been associated with higher PTH levels in non-dialysis CKD patients with SHPT, especially among those who also show signs of malnutrition and inflammation [214]. Confirmation of these apparently conflicting observations across other CKD populations, together with a clearer characterization of the underlying mechanisms, is required before intentional WL can be recommended as a therapeutic strategy for SHPT in CKD. These findings echo earlier work [215].

Eating Behavior Profile: anorexia; altered taste perception; reduced caloric intake; food aversion and avoidance.

7.3. Hypoparathyroidism

PTH exerts direct actions on bone resorption and on renal transport of calcium (Ca) and phosphorus, as well as indirect actions on the intestine, where it enhances Ca absorption through increased production of the active form of vitamin D, 1,25-dihydroxycholecalciferol ($1,25(OH)_2D$) [2,216]. Hypoparathyroidism (HypoPT), characterized by low PTH levels and hypocalcemia (among other alterations), has been less studied with respect to EB and BW. Chronic hypocalcemia, however, can cause neurological symptoms such as irritability, depression, and brain fog—all of which may influence appetite and food choices [217,218]. Brain fog may be defined as an altered state of consciousness in which a person is less wakeful, aware, alert, and focused than usual [219]. Patients with HypoPT may thus present with poor appetite and WL [220,221,222]. While HypoPT is more often associated with reduced appetite and WL [220,221,222], the opposite presentation—excessive OB in infancy—points to a different set of concerns. Importantly, patients who develop excessive OB within the first year of life should be considered at high risk for monogenic disorders, including mutations involving guanine nucleotide-binding protein, alpha-stimulating gene exons 1–13 [223,224,225].

Eating Behavior Profile: reduced appetite in the context of cognitive impairment.

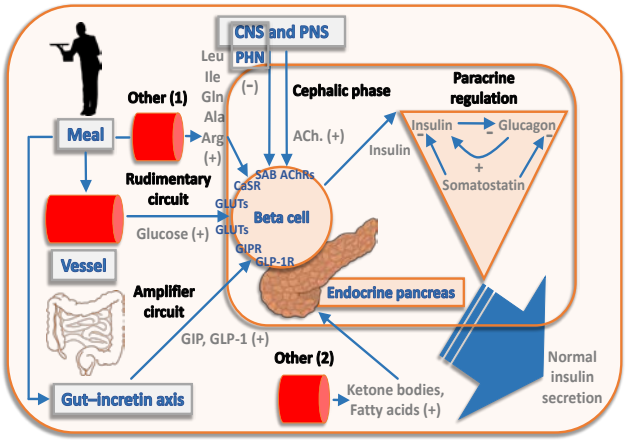
8. Glycemic Disturbances

The extraordinary advances to date in the understanding of the histophysiology of the pancreatic islets—first described by Paul Langerhans (1847–1888) in the nineteenth century (1869)—have enabled an integrated and multidimensional view of insulin regulation, the principal hormone of glycemic homeostasis [69]. This regulation involves a cascade of mechanisms, beginning with the main insulin secretagogue (ingested glucose), other nutrient stimuli (e.g., amino acids and fatty acids), incretin hormones such as GLP-1 and GIP (which enhance insulin secretion), and the paracrine interactions within the endocrine pancreas (e.g., glucagon from α-cells stimulates insulin secretion, whereas somatostatin from δ-cells

inhibits it).

In addition to the tightly regulated secretory control of insulin, the complex cephalic phase of insulin secretion must also be considered. This phase refers to the early release of insulin triggered by food-related sensory stimuli acting on receptors in the head and oropharynx, likely mediated by neural pathways [226]. Evidence supporting this neuronal mediation includes the observation that insulin release during this phase is inhibited by trimethaphan (a ganglionic blocker acting via nicotinic receptor antagonism), muscarinic acetylcholine receptor antagonists, and vagotomy (Figure 5) [226,227]. Studies in mice with targeted mutations in M_3 muscarinic acetylcholine receptors (M3Rs) further suggest that β-cell M3Rs play a central role in promoting insulin secretion and maintaining glucose homeostasis [228].

Although not depicted in Figure 5 below, the vascular endothelium contributes to insulin action, and tissue-specific endothelial cells are critical for maintaining homeostasis in pancreatic islets and many other tissues [229,230]. The amino acids L-leucine, L-isoleucine, L-glutamine, L-alanine, and L-arginine are particularly important for stimulating β-cell electrical activity and thereby promoting insulin secretion [231]. The CaSR functions as a pancreatic nutrient sensor and is expressed in non-calciotropic tissues such as pancreatic α- and β-cells [232]. In the gut, CaSR coordinates digestion and nutrient absorption, among other roles [233]. The glucose-dependent insulinotropic polypeptide receptor (GIPR) is a member of the class B (class 2) glucagon receptor subfamily of G protein–coupled receptors, which also includes the GLP-1 receptor (GLP-1R) [234,235,236].



CNS: central nervous system; **PNS**: peripheral nervous system; **PHN**: paraventricular hypothalamic nucleus; **SAB**: sympathetic autonomic branch; **ACh**: acetylcholine; **AChRs**: acetylcholine receptors; +: stimulation; -: inhibition; **Leu**: L-leucine; **Ile**: L-isoleucine; **Gln**: L-glutamine; **Ala**: L-alanine; **Arg**: L-arginine; **CaSR**: calcium sensing receptor; **GLUTs**: glucose transporters (e.g., GLUT1 and GLUT3 are mainly expressed in human β-cells [237]); **GIP**: glucose-dependent insulinotropic polypeptide; **GIPR**: glucose-dependent insulinotropic polypeptide receptor; **GLP-1**: glucagon-like peptide-1; **GLP-1R**: glucagon-like peptide-1 receptor.

Figure 5. Diagram of the major pathways regulating insulin secretion

Building on these molecular insights into insulin action, it is worth noting that the identification of the pancreatic β-cell as the site of insulin secretion is relatively recent, even though the clinical recognition of diabetes mellitus (DM) dates back to antiquity. DM is an endocrine disease that affects more than 400 million people worldwide [232,238]. Type 1 diabetes mellitus (T1DM) is defined by an absolute deficiency of insulin, whereas T2DM involves a relative deficiency. Individuals with T2DM do not require insulin for survival but often need it to achieve optimal glycemic control—typically fasting glucose levels of 70-99 mg/dL, remaining below the renal threshold for glucose (≈180-200 mg/dL) and without glycosuria [239]. In such cases, the condition is referred to as insulin-requiring DM.

Furthermore, it is important to note that amylin—a 37-amino-acid peptide also known as islet amyloid polypeptide—is a pancreatic β-cell hormone co-secreted with insulin in response to nutrient stimuli [240,241,242]. As an anorectic hormone, amylin contributes to feeding-related changes in neuronal activity within key structures of the gut–brain axis [241]. Abnormal amylin production is a hallmark peripheral pathology in both the early (pre-diabetic) and late phases of T2DM, where hyperamylinemia (early phase) and hypoamylinemia (late phase) coincide with hyperinsulinemia and hypoinsulinemia, respectively [243]. In the late phase of T2DM, amylin may also form amyloid aggregates in the brain, potentially facilitating central Aβ amyloid formation and contributing to neurodegenerative processes [243]. Consistent with these findings, recent studies have shown a higher incidence of Alzheimer disease (AD) in individuals with T2DM compared to those without the condition [244]. Extending these insights—and based on overlapping mechanisms such as central IR, amyloid accumulation, and neuroinflammation—AD has been proposed as a form of type 3 diabetes, confined primarily to the brain [239,245]. As AD progresses, patients frequently develop significant eating difficulties—particularly once they become fully dependent in their activities of daily living—often requiring specialized nutritional support [246].

Armed with the knowledge summarized above regarding the complex regulation of insulin secretion, the physician can attempt to recreate these physiological circuits—e.g., reducing the impact of glucose intake through dietary guidance and enhancing the gut–incretin axis by using vildagliptin, an incretin-related drug [247]. Vildagliptin is a highly selective, orally active inhibitor of dipeptidyl peptidase-4, the enzyme responsible for the inactivation of GLP-1, a naturally occurring incretin hormone, as mentioned above [247,248].

The so-called incretin effect refers to the phenomenon in which insulin secretion is significantly greater when glucose is administered orally or enterally compared to an isoglycemic intravenous glucose infusion [249]. This effect is attributed to the release of the incretin hormones such as GLP-1 and GIP from the gut [249]. Incretins thus amplify insulin secretion [250].

However, daily medication use cannot perfectly replicate the physiological regulation of insulin secretion, often resulting in side effects such as hypoglycemia (blood glucose less than 70 mg/dL). The alternating cycles of hyperglycemia and hypoglycemia, with only limited periods of normoglycemia, can lead to changes in EB and BW, as discussed below.

8.1. Diabetes Mellitus

Because physiological insulin secretion is no longer finely regulated (see previous section), people with T1DM mainly treated with insulin—the most potent hypoglycemic agent—and those with T2DM receiving sulfonylureas, such as glimepiride or gliclazide (oral hypoglycemic agents), and/or a biguanide such as metformin (an antihyperglycemic agent), or newer agents, live with the constant dual risk of glycemic extremes—from hyperglycemia to hypoglycemia—while striving to maintain near-normoglycemia. As an aggravating factor, cardiovascular disease remains the leading cause of morbidity and mortality in DM [251].

Chronic insulin deficiency, worsened by elevated counter-regulatory (or counter-insulin) hormones such as glucagon, can precipitate a life-threatening metabolic cascade characterized by sustained hyperglycemia, increased plasma osmolarity, osmotic diuresis, polyuria, polydipsia, dehydration, polyphagia, WL, negative potassium balance, muscle weakness (or dynapenia), reduced LPL (an extracellular enzyme), hyperlipidemia (especially hypertriglyceridemia), accelerated lipolysis via hormone-sensitive lipase (an intracellular enzyme), increased availability of free fatty acids as substrates for hepatic ketogenesis, and progressive accumulation of hepatic ketone bodies (KBs) (acetoacetate, 3-β-hydroxybutyrate, and acetone) [122,252,253,254,255,256]. Increased circulating KBs trigger nausea, abdominal pain, and vomiting (see definitions of nausea and vomiting in Table 1); this can compound the already existing fluid- and electrolyte-depleted state [257]. As acidosis deepens, patients may develop Kussmaul respiration, fruity breath, and ultimately impaired consciousness up to coma (total or partial loss of consciousness, voluntary motor function, and sensation) [253]. Diabetic ketoacidosis (DKA) is therefore a critical, potentially fatal acute complication in both T1DM and T2DM whose pathophysiology must be understood to ensure effective treatment [258]. However, DKA is more common in new-onset or poorly controlled T1DM [254].

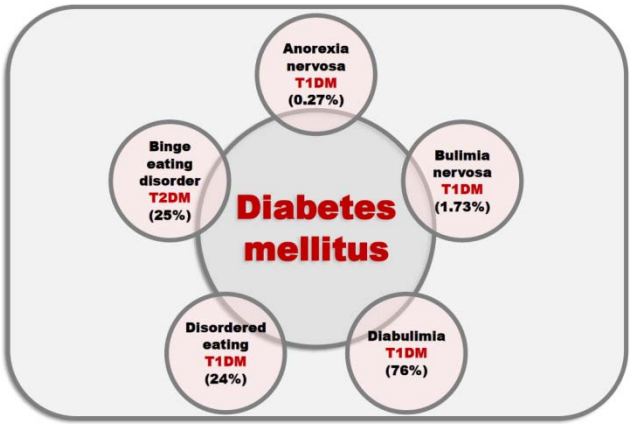
Disordered eating (DE), especially subthreshold forms, is common in both T1DM and T2DM and is associated with poorer glycemic control, higher complication rates, and increased mortality [259]. Importantly, the likelihood of diabetic retinopathy is nearly threefold higher in the presence of disordered EBs [260]. Eating disorders are about twice as prevalent in young women with T1DM compared with peers without diabetes [261]. Additionally, a hospital-based study from Jamia Hamdard University in New Delhi, India, reported a lower prevalence of eating disorders among patients with T2DM than that reported from high-income Western countries [262].

Despite being able to eat freely, people with DM face several challenges in adhering to their dietary regimen, including the need for careful food planning and constant glycemic self-monitoring; denial of the disease's severity; poor understanding of the diet–disease relationship; misinformation; lack of social support; and feelings of dietary deprivation, among others [263].

Therefore, every consultation should be an opportunity to educate people with DM about daily glycemic monitoring, fostering self-assessment and self-management [264]. It is essential to identify restrictive EBs, episodes of overeating, dietary under-reporting, and poor adherence to dietary recommendations, which can lead to suboptimal metabolic control, and to take steps to correct them [263]. However, detecting these problems requires specific training, and eating disorders often go unrecognized in diabetes care settings because clinicians may be unaware that DE and WL behaviors can underlie treatment noncompliance and unexplained metabolic impairment in their female patients [265].

In this context, diabulimia is an emerging DE behavior (Figure 6) characterized by the intentional omission or restriction of insulin by people with T1DM to control weight [266,267,268,269,270,271]. Although it is not listed as a distinct diagnostic category in the DSM-5, diabulimia represents a high-risk behavior that substantially increases the likelihood of both acute and chronic diabetes complications—including DKA, retinopathy, neuropathy—and premature mortality [44,268].

The following subsections address chronic complications of DM that have important repercussions on EB and BW, including diabetic gastroparesis (8.2), insulinoma-induced hypoglycemia (8.3), and diabetic neuropathic cachexia (8.4). Regardless of the underlying cause, the clinical manifestations of hypoglycemia are always acute and emergent, requiring prompt healthcare personnel attention. Recognizing these manifestations is essential for both diabetologists and nutritionists, as timely intervention can prevent serious complications—though in many mild cases, a simple cup of hot coffee with sugar will do.



T1DM: type 1 diabetes mellitus; **T2DM:** type 2 diabetes mellitus.

Note. Percentages represent reported prevalence within the specified diabetes subtype. The 76% value refers to insulin omission among individuals with T1DM who exhibit disordered eating behaviors.

Figure 6. Diagram showing the prevalence of eating behavior alterations in diabetes mellitus Adapted from [267]

Eating Behavior Profile: polyphagia; nausea, abdominal pain, and vomiting (particularly in uncontrolled hyperglycemic states); restrictive eating and binge-type behaviors.

8.2. Diabetic Gastroparesis

Diabetic gastropathy is a symptom complex of gastric neuromuscular dysfunction—encompassing functional, contractile, electrical, and sensory abnormalities—

associated with DM [272,273]. Its traditional manifestation is diabetic gastroparesis (DG), characterized by delayed gastric emptying [272,273]. DG occurs in T1DM and T2DM, although it is substantially less common in T2DM [272,273]. The estimated 10-year cumulative incidence is approximately 5.2% in T1DM compared to 1% in T2DM [274,275]. The major clinical features of DG include early satiety, loss of appetite, nausea, vomiting, epigastric discomfort, and bloating. WL, however, is reported inconsistently: some authors consider it uncommon, whereas others note that reduced caloric intake in DG patients may lead to significant WL [276,277].

The pathophysiology of DG is complex and involves multiple factors, with proposed mechanisms including chronic hyperglycemia, vagal nerve dysfunction, disruption of the interstitial cells of Cajal network (specialized pacemaker cells coordinating gastric motility), reduced expression of neuronal nitric oxide synthase in the myenteric plexus, and increased oxidative stress [278,279]. Management focuses on achieving adequate glycemic control and enhancing gastric motility with prokinetic agents, such as domperidone—a type II dopamine receptor antagonist—complemented by dietary modifications and, in selected cases, emerging therapies under investigation [275,276].

Eating Behavior Profile: early satiety; reduced appetite; nausea and vomiting; epigastric discomfort; bloating.

8.3. Insulinoma-Induced Hypoglycemia

Insulinoma is a rare functional pancreatic neuroendocrine tumor, with an incidence of about 4 cases per million person-years [280,281]. It is characterized by autonomous and excessive insulin secretion, leading to recurrent hypoglycemia with symptoms such as confusion, sweating, and palpitations [281]. More than 80% of insulinomas are solitary and benign; 7–10% are multiple, often in association with multiple endocrine neoplasia type 1 [282,283].

The diagnostic hallmark of insulinoma was first described by Allen Oldfather Whipple (1881–1963) in 1935 and is known as “Whipple triad,” or descriptively as the “triad of insulinoma” [282,284,285]. It comprises three features: hypoglycemia-induced symptoms, low blood glucose during episodes, and symptom relief following glucose administration [282].

Most patients with insulinoma develop symptoms 8–10 hours after their last meal, and to relieve these symptoms, they often increase their caloric intake, which can lead to WG [286]. During a hypoglycemic episode, increased sweating, tingling, and hunger sensation are mediated by activation of the cholinergic system, whereas nervousness and anxiety are triggered by the catecholaminergic system, imparting urgency to FI [287]. In some cases, these compensatory EBs may mimic serious eating disorders, such as binge-eating-like behavior [288].

Although distinct from diabulimia, both conditions illustrate how dysregulated glucose metabolism can drive abnormal eating—insulinoma by triggering eating via pathological hypoglycemia, and diabulimia by resulting from intentional insulin restriction.

Metabolically, hypoglycemia in insulinoma arises primarily from reduced hepatic glucose output rather than from increased peripheral glucose utilization [283,289]. Consequently, it tends to occur predominantly during fasting, when hepatic glucose output becomes the major determinant of glucose homeostasis [283]. Insulin suppresses hepatic glucose production by inhibiting glycogenolysis (the breakdown of glycogen) and gluconeogenesis (the synthesis of glucose from non-carbohydrate substrates), while concurrently promoting glycogen synthesis [290]. By blocking glycogenolysis (a catabolic pathway) and gluconeogenesis (an anabolic pathway), and stimulating glycogenesis (another anabolic pathway), insulin sharply limits the amount of glucose released into the circulation [291,292]. These coordinated actions underpin the biochemical profile and clinical presentation of insulinoma and form the physiological rationale for both diagnostic assessment and therapeutic strategies.

Clinical observations illustrate these pathophysiological effects. In a report of four patients undergoing surgery for benign insulin-secreting tumors [293], hypoglycemia manifested as chronic neuroglycopenic symptoms, including confusion, personality changes, blurred vision, and loss of consciousness; one patient experienced an inaugural hypoglycemic coma. The most common adrenergic symptoms were asthenia, headache, sweating, and tachycardia, all alleviated by oral glucose administration. All four patients reported WG, with an average BMI of 34.3 kg/m². Indeed, insulin hypersecretion is well known to promote fat accumulation [294].

In a retrospective study of 76 patients diagnosed with insulinoma between 2010 and 2020—including 48 females and 28 males, with a mean age at diagnosis of 52 years—the most frequent symptoms were loss of consciousness (68%), sweating (59%), vertigo (56%), and WG (36%) [295].

A case report of a 24-year-old male medical student with insulinoma described hypoglycemic episodes predominantly during fasting and after exercise [296]. The patient also reported increased appetite and gained nearly 20 kg over six months [296].

In contrast, a 94-year-old woman with insulinoma presented without episodes of diaphoresis (profuse sweating) or impaired consciousness and had no recent changes in weight [50,297]. Her appetite varied, appearing to fluctuate with her mood [297]. When insulinoma manifests primarily with behavioral changes, it can be mistaken for a psychiatric disorder [298].

Among 59 patients with insulinoma (mean age, 55 years), 42 (71%) reported symptom relief with food intake, 23 (39%) WG, 8 (14%) hunger, and 7 (12%) WL [299]. Although WG is more common, WL may occur, particularly when patients restrict food intake to control symptoms or when the tumor is malignant [300,301].

Collectively, these reports indicate that insulinoma consistently affects EB and BW, although manifestations are heterogeneous. Hypoglycemia often drives increased FI, particularly during fasting or after exercise, leading to hyperphagia and significant WG in many cases. Insulin’s anabolic effects—enhancing glycogen synthesis and promoting fat storage—further contribute to WG. However, some patients, especially older individuals, may

show minimal changes in appetite or weight, and behavioral symptoms can mimic psychiatric conditions. Overall, EB and BW alterations in insulinoma reflect a complex interplay between biochemical mechanisms and individual patient factors such as age, metabolic reserve, and symptom perception.

Eating Behavior Profile: intense hunger with urgency to eat; binge-like eating behaviors; neurobehavioral changes mimicking psychiatric conditions.

8.4. Diabetic Neuropathic Cachexia

Diabetic neuropathic cachexia (DNC), first described by Max Ellenberg in 1974, is a rare syndrome associated with poorly controlled DM [302,303,304,305]. It predominantly affects men with T2DM in their sixth to seventh decades of life, but can affect both types of DM and occurs irrespective of the duration of the DM [306,307]. It is characterized by substantial unintentional WL and the abrupt onset of a symmetric, painful peripheral neuropathy with preserved motor strength [304,305].

Thus, DNC is a syndrome marked by symmetrical peripheral neuropathy, severe WL (up to 60% of BW), and painful dysesthesias, typically affecting the proximal lower limbs, hands, or lower trunk [308]. The pain is usually burning in quality and often accompanied by allodynia–pain sensation generated by low threshold [305,309]. Patients experience significant and rapid WL, marked by emaciation of fat and muscle mass, defining the cachectic state (Table 1) [304,305,310].

Marked cutaneous hypersensitivity often renders patients unable to tolerate even light contact, including the touch of bed sheets. As noted, they typically appear severely emaciated and malnourished; oral hypoglycemic agents are ineffective, so insulin is required for glycemic control, with management usually combining insulin therapy, a high-protein diet, and analgesics (e.g., carbamazepine, a tricyclic compound of the dibenzazepine class, or pregabalin, a gamma-aminobutyric acid (GABA) analogue, among others) [308,311,312,313,314].

Because deficits span all energy-providing macronutrients (i.e., carbohydrates, fats, and proteíns), the malnutrition is proportionate and adopts a marasmic (starvation) pattern in adults [315]. Behaviorally, however, the presentation shows little variability: most patients report anorexia (loss of appetite) [302,303,304,310] [316,317,318,319] [320,321,322,323].

Despite this severe presentation, the prognosis is generally favorable, with most patients regaining their baseline weight and experiencing resolution of painful sensory symptoms within one or two years [302,303,304,305,308,323,324].

Eating Behavior Profile: profound anorexia reflecting a marasmic (starvation-type) pattern.

9. Hypothalamic-Pituitary-Ovarian Disorders

Figure 1 schematically illustrates the hypothalamic–pituitary–ovarian (HPO) axis. From puberty and adolescence (≈8–18 years) through the reproductive years and into menopause (≈50 years)—typically preceded by perimenopause in the 40s—female physiology is largely regulated by two principal families of sex hormones: estrogens (Es) and progestogens. The main Es, with subscripts indicating the number of hydroxyl groups, are estradiol (E_2, the most potent), estrone (E_1, of intermediate potency), and estriol (E_3, the least potent). Progestogens comprise the natural hormone progesterone (P) as well as its synthetic analogues, the progestins. Estetrol (E_4), the estrogen of fetal life, is produced by the fetal liver and is present only during pregnancy, reaching relatively high concentrations in the fetus and lower concentrations in the maternal circulation; notably, it is found only in humans and appears as early as 9 weeks of gestation [325].

Thus, the menstrual cycle represents the coordinated clinical expression of dual estrogen–progesterone influence, with Es predominating in the first (follicular) phase and P in the second (secretory or luteal) phase [326]. Their roles are particularly pronounced during pregnancy, when P supports implantation and promotes maternal immune tolerance of the fetus.

In practical terms, when the balance between these hormones is disturbed, characteristic clinical conditions emerge. For instance, relative fluctuations of Es and progestogens underlie premenstrual syndrome (PMS) and influence the choice of hormonal contraception (e.g., combined estrogen–progestin versus progestin-only formulations). Beyond these cyclical disturbances, more chronic dysregulation gives rise to syndromes such as polycystic ovary syndrome (PCOS), first described in 1935 by Irving Freiler Stein (1887–1976) and Michael Leo Leventhal (1901–1971), which has since become one of the most common endocrine disorders in premenopausal women [69,327,328,329,330,331].

Accordingly, this section reviews alterations in EB and BW associated with PMS (9.1), contraceptive use (9.2), and PCOS (9.3).

9.1. Premenstrual Syndrome

PMS comprises recurrent physical, emotional, cognitive, and behavioral symptoms that typically emerge during the luteal phase, 10–14 days before menstruation, and resolve with the onset of bleeding; these symptoms can negatively affect women's daily functioning and quality of life [332,333]. The physical manifestations often include headache, breast tenderness, abdominal bloating, peripheral edema, fatigue, and WG, whereas the psychological and behavioral symptoms frequently involve irritability, mood swings, increased appetite, food cravings, social withdrawal, anxiety, and depressed mood [332,334,335]. Importantly, PMS should be distinguished from premenstrual dysphoric disorder, a more severe condition characterized by disabling affective symptoms (e.g., marked irritability, hopelessness, and mood disturbances) and formally recognized in the DSM-5 [44,334]. Within this review, the emphasis is placed on eating-related symptoms—particularly appetite, cravings, and EB. In this context, PMS is notably associated with premenstrual cravings for sweets, increased appetite, and indulgence in refined sugar [336].

The pathophysiology of PMS remains complex, imprecise, and not fully understood [337]. Several factors may influence the development and severity of PMS symptoms, including genetic predisposition, familial history, variations in female sex hormones (further discussed below), neurotransmitters (e.g., serotonin, opioids, and catecholamines) and their metabolic cofactors (e.g., pyridoxine or vitamin B_6 is required for the synthesis of serotonin), inflammatory mediators, and coexisting psychological conditions [338,339,340,341,342].

Some authors propose that a higher estrogen-to-progesterone ratio—resulting from relatively elevated E or reduced P levels—may contribute to PMS symptoms such as mastalgia, premenstrual anxiety, and menorrhagia [340,343,344]. In this view, the effects of E may not be sufficiently counterbalanced by P, leading to water retention and mood changes [340,343,344]. Other investigators, however, report that women with PMS do not exhibit higher E or P concentrations than the general population, and widely accepted explanations for why some women are more sensitive to hormonal fluctuations remain lacking [334].

Experimental evidence supports, however, a role of female hormones in fluid and energy balance: in ovariectomized albino rats, Es inhibit both food and water intake, whereas P promotes water intake without affecting BW [345]. Similarly, in humans and other species, Es suppress FI and enhance spontaneous activity [346]. Additionally, on the one hand, E_2 increases the release of satietogenic hormones such as CCK, insulin, and leptin—thereby reducing FI; on the other hand, it inhibits the release of ghrelin in the stomach [347]. In contrast, the progesterone-induced increase in appetite is not mediated by ghrelin; in fact, P injection (1 mg) in ewes decreases ghrelin concentration, whereas its simultaneous administration with GH (0.01 mg) increases it [348]. Energy intake appears to be lower in the follicular phase than in the luteal phase, with a particularly marked decrease in the days leading up to and including ovulation [349]. Table 2.

It is important to note that DM increases the incidence of PMS by disrupting the physiological levels of E, P, serotonin, GABA, as well as by inducing gut dysbiosis, which may further exacerbate PMS severity [350].

The therapeutic scenario of PMS remains elusive. Clinical trials have neither confirmed nor refuted the efficacy of P as a treatment [351]. Likewise, vitamin B_6 supplementation has been proposed for managing PMS, though evidence supporting its effectiveness remains limited [352].

Table 2. Eating-Related Symptoms in Premenstrual Syndrome

Study description	Symptoms and outcomes	Refs.
Seventy-six women, with a mean age of 35 ± 7 years, who reported premenstrual cravings for sweet foods in a retrospective questionnaire, were prospectively assessed using a pre- and postmenstrual eating questionnaire, along with daily ratings of craving, mood, irritability, and breast tenderness over two menstrual cycles	Perimenstrual food cravings were reported by 72% of participants, with cravings confined to the menstrual phase in 13%	[353]
A cross-sectional study was conducted with 27 students from a public university in Mato Grosso do Sul, Brazil. Food intake was assessed using a 24-hour dietary recall, nutritional status was evaluated through anthropometric measurements, and food cravings were measured using the Food Desire Questionnaire	The desire for foods rich in sugar, salt, and fat—such as chocolate, pastries, snacks, and desserts—was higher during the premenstrual period; however, this increase was not accompanied by higher energy intake or changes in macronutrient distribution	[354]
This study enrolled 60 obese women with PMS, divided into a younger group (18–39 years) and an older group (40–48 years), each compared with an age-matched healthy control group. Each group included 30 women. Serum leptin levels were measured in all participants. Nervousness, a psychosomatic symptom of PMS, was assessed using a numerical rating scale	PMS is strongly associated with obesity and has been linked to elevated serum leptin levels, which, in turn, were associated with increased anxiety	[355]

Refs: references.

Eating Behavior Profile: increased appetite; premenstrual food cravings (particularly for sugar, salt, and fat); increased consumption of refined carbohydrates.

9.2. Contraceptive-Related Changes

The effects of Es and P on EB and BW were outlined in the previous subsection; however, several additional aspects warrant further consideration. Es reduce appetite and FI through central mechanisms, yet they may increase BW—partly owing to hydromineral (fluid) retention—and promote redistribution of fat to the gluteofemoral region [356,357]. In contrast, P increases appetite, FI, and BW in the presence of Es [356]. Progestins likewise stimulate appetite and WG and exert anabolic effects [356]. Testosterone, the principal human androgen—synthesized mainly by testicular interstitial (Leydig) cells and also produced by the adrenal glands and ovaries—increases appetite and FI via central mechanisms, may promote overeating, favor accumulation of abdominal (visceral) fat, and increase lean body mass [356,358,359].

The risk of OB is higher among users of hormonal contraceptives compared with those using non-hormonal methods [360,361]. Moreover, significant WG is almost always attributable to a substantial increase in FI [362].

However, all in all, Es are rather widely recognized for their protective effects against metabolic dysregulation, including their anti-obesogenic properties [363]. E_1, E_2, and E_3 undergo extensive metabolism primarily through phase I (hydroxylation, oxidation, and reduction) and phase II (primarily conjugation) reactions, whereas E_4 undergoes only phase II reactions [364]. Thus, E_4 is minimally metabolized—if at all—and is not reconverted to E_3 or E_2 [365]. It is not associated with clinically relevant effects on BW and is unlikely to cause WG; indeed, the proportion of women gaining or losing ≥ 2 kg during treatment was similar between those receiving E_4/drospirenone (a synthetic progestin) 15 mg/3 mg and

those receiving E_2 valerate/dienogest (a combination in which dienogest likewise acts as a progestin) [366,367,368]. Other studies further suggest that E_4 may even help prevent WG [369].

Eating Behavior Profile: estrogens tend to reduce appetite; progestogens and androgens tend to increase appetite.

9.3. Polycystic Ovary Syndrome

PCOS, also known as Stein–Leventhal syndrome, is one of the most common endocrine disorders affecting women of reproductive age [370]. The two aforementioned authors, in their seminal report entitled "Amenorrhea associated with bilateral polycystic ovaries" (1935), laid the foundation for identifying this distinct endocrine and reproductive disorder [371,372]. In their historical case series of seven patients, three were obese, one was thin, three had no mention of BW, and no eating-related symptoms were reported [372]. Since that first description, however, BW patterns in PCOS have proven heterogeneous, encompassing OB, normal weight (NW), and thinness. Accordingly, this subsection provides a current overview of eating and body weight disorders in PCOS.

Several studies have consistently reported a higher risk and prevalence of DE (e.g., binge-eating symptomatology) and eating disorders (e.g., bulimia nervosa) among patients with PCOS [371,372,373,374] [375,376,377] [378,379,380]. Nevertheless, food craving—a characteristic feature of this syndrome—represents a transdiagnostic process that underlies clinically significant disordered EBs and eating disorder diagnoses, thereby supporting the need for routine screening for such conditions [376,378,381]. For greater clarity, a transdiagnostic process refers to a mechanism that occurs across different disorders and acts as either a risk factor or a maintaining factor for the condition [382].

In the U.S., some studies report that the prevalence of overweight and OB among women with PCOS is as high as 80% [383]. Outside the U.S., however, the prevalence of OB in affected women is lower, although it has increased over time, with studies reporting rates as low as 20% [383]. As previously mentioned, PCOS may manifest with diverse weight patterns, and research often compares NW women with PCOS to their lean and obese counterparts. NW women are more likely to be older at diagnosis and to present with polycystic ovaries, suggesting that PCOS in these cases represents part of a continuous clinical spectrum rather than a distinct entity [384]. Other variations in presentation among groups are largely attributable to differences in BW [384,385]. In this regard, the reader is kindly referred to a recent narrative review on the topic [386]. In lean women with PCOS, hormonal, metabolic, and hematological profiles are altered compared with healthy counterparts, but these derangements are generally comparable to or less pronounced than those observed in obese women with PCOS [387].

The pathophysiology of PCOS remains poorly understood and continues to pose a challenge. Nevertheless, there is a complex interplay between PCOS, IR, OB, and features of the metabolic syndrome (MS). The relationship among these conditions is multifaceted and often bidirectional: IR exacerbates hyperandrogenism and ovulatory dysfunction, while PCOS itself increases the risk of developing impaired glucose tolerance and T2DM [388].

Eating Behavior Profile: disordered eating patterns (particularly binge-eating symptomatology); increased food cravings.

10. Adrenal Diseases

The hypothalamic–pituitary–adrenal (HPA) axis is schematically depicted in Figure 1. Corticotropin-releasing hormone (CRH), a 41-amino-acid neuropeptide primarily secreted by the paraventricular nucleus of the hypothalamus, stimulates the release of adrenocorticotropic hormone (ACTH), a 39-amino-acid peptide, from the AP. ACTH, in turn, initiates the first enzymatic step of adrenal steroidogenesis through activation of the human cholesterol side-chain cleavage enzyme, cytochrome P450scc, which converts cholesterol to pregnenolone [389,390,391] [392,393,394]. Pregnenolone serves as the precursor of all known steroid hormones, and its synthesis from cholesterol via P450scc constitutes the rate-limiting step in steroid hormone production [395].

HPA axis is essential for survival, critically coordinating metabolism and water–electrolyte homeostasis. The adrenal cortex secretes cortisol—the prototypical glucocorticoid—from the middle zona fasciculata; aldosterone—the principal mineralocorticoid—from the outer zona glomerulosa; and dehydroepiandrosterone sulfate from the inner zona reticularis, an adrenal androgen that serves as a precursor for peripheral testosterone and other sex steroids [396,397].

This section reviews disturbances in EB and BW associated with three adrenal hypersecretion syndromes and one hyposecretion syndrome—Cushing syndrome (glucocorticoid excess, 10.1), adrenal insufficiency (steroid hyposecretion involving cortisol and aldosterone in primary adrenal insufficiency, 10.2), primary aldosteronism (Conn syndrome; aldosterone excess, 10.3), and pheochromocytoma (catecholamine excess arising from the adrenal medulla, 10.4) [398].

10.1. Cushing Syndrome

It is essential to begin this subsection by defining allostasis, a concept that refers to the achievement of stability through change [399]. Introduced by P. Sterling and J. Eyer in 1988, this term was coined to clarify ambiguities associated with the word "stress" [399,400,401]. Allostasis describes the process by which homeostasis—previously defined above—is maintained, while recognizing that physiological set points (i.e., the levels around which regulated systems are adjusted, such as blood pressure, body temperature, or cortisol concentrations) and other regulatory boundaries may shift in response to environmental conditions [2,399,402,403]. The primary mediators of this adaptive process include hormones of the HPA axis (e.g., cortisol), catecholamines

(e.g., adrenaline), the parasympathetic nervous system, and both pro- and anti-inflammatory cytokines [399,400,404]. Axes such as the HPA axis operate to maintain these physiological set points [405].

For example, an elevated cortisol set point helps explain the persistently high cortisol levels observed in Cushing syndrome (CS)—the general term for cortisol excess—and in Cushing disease (CD), which specifically arises from a pituitary adenoma. In CD, the corticotroph cells of the pituitary adenoma are reset to a higher-than-normal feedback set point, rendering them less sensitive to glucocorticoid (GC) inhibition. This mechanism has important clinical implications: dexamethasone suppression testing—a diagnostic procedure that uses the synthetic glucocorticoid dexamethasone—can help distinguish pituitary (CD) from ectopic sources of ACTH. Pituitary-driven disease typically shows partial suppression, whereas ectopic ACTH secretion is usually markedly resistant to GC negative feedback [406,407,408,409].

The circadian rhythmicity—i.e., biological rhythms with a periodicity of approximately one day—of plasma glucocorticoids (GCs) has been well characterized in both humans and rats, with extensive evidence indicating daily rhythmicity at every level of the HPA axis [2,410]. The diurnal variation of the HPA axis stress response appears to be closely related to FI as well as basal activity [410]. However, CS is marked by disruptions in this rhythmicity, among other alterations [410]. Elevated cortisol levels stimulate appetite in humans, and GC infusions have been shown to increase caloric intake in both humans and rats [411,412]. The nighttime elevation of cortisol might also contribute to awakenings to eat, as observed in night eating syndrome [413]. Neurobiologically, GC excess stimulates the orexigenic NPY while inhibiting the anorexigenic CRH; together, these effects promote appetite and WG, contributing to the OB of CS [414,415,416]. Moreover, GCs also promote food-seeking behavior—particularly for foods rich in fat and sucrose—and induce specific cravings that resemble those elicited by stress, ultimately leading to increased BW and preferential central fat accumulation [402,413,417] [418,419,420,421]. Indeed, GCs heighten the salience of pleasurable or compulsive activities (e.g., ingesting sucrose, fat, and drugs, or wheel-running), thereby motivating the consumption of such “comfort foods” and contributing to the systemic increase of abdominal fat depots [422]. Consequently, the phenotype of CS is characterized by abdominal and truncal fat accumulation with reduced lean body mass, together with multiple features of the MS—IR, dyslipidemia, hypertension, hypercoagulability, and hypercytokinemia—among others [423].

Contrary to the detailed description of DE in CS presented above, patients with this syndrome may not exhibit overtly abnormal EB; rather, a modest increase in appetite is often observed, and their eating patterns tend to resemble those of individuals with mild OB [424]. However, the mechanisms underlying WG in CS are considerably more intricate.

CS is a well-recognized endocrine cause of OB [425,426,427]. A notable proportion of obese patients—approximately 9.3%—are found to have CS [428]. As outlined by Orth et al., the most common sign of CS is progressive COB, characterized by preferential fat accumulation in the face, neck, and trunk, while the extremities are spared or even wasted [429]. In adults, this pattern rarely leads to generalized OB, whereas in children it is almost the rule. The reported incidence of COB in CS ranges from 79% to 97%.

More recently, CS has also been regarded as a clinical model for investigating sarcopenic obesity (SOB), as it shares several defining features with this relatively new pathological condition—namely, the coexistence of low lean body mass (or muscle atrophy) and increased fat mass, dynapenia (i.e., reduced muscle strength, occurring in over half of CS patients), and elevated circulating levels of the pro-inflammatory cytokine interleukin-6 [430,431,432,433,434,435]. The inclusion of CS in the study framework of SOB has renewed interest in the former condition, yielding indisputable insights into its convergent pathophysiology.

Of note, an important consideration concerns a very rare form of CS—accounting for fewer than 2% of all cases—caused either by a unilateral adrenal adenoma or by primary bilateral macronodular adrenal hyperplasia [436,437,438]. In this variant, cortisol secretion becomes stimulable by FI, giving rise to the expression food-dependent CS [436,437]. Here, physiological postprandial increases in GIP abnormally trigger cortisol release because the pathological adrenal tissue ectopically expresses the non-mutated GIP receptor, leading to the alternative designation GIP-dependent CS [436].

GIP is considered a pro-anabolic hormone with significant effects on AT [439]. For example, it promotes lipid uptake, lipogenesis, and fat accumulation [436]. Conversely, reduced GIP receptor expression impairs these metabolic processes and contributes to IR and OB [436]. Dysmetabolism may be defined as a pathological state of energy distribution and storage [440]. Indeed, OB is considered a dysmetabolic state because it is strongly associated with a cluster of metabolic dysfunctions and health risks, including—not only IR but also high blood pressure and abnormal lipid levels—among others [441]. Experimental evidence further suggests that enhancing GIP receptor activity (through agonism) may confer metabolic benefits—such as improving dyslipidemia and atherosclerosis—independently of BW loss [442,443].

In contrast to the hypercortisolism of CS, adrenal insufficiency (AI) represents the opposite end of the spectrum of GC action, with equally profound effects on energy balance, metabolism, and EB, as detailed in the following subsection.

Eating Behavior Profile: increased appetite and caloric intake; night eating–type behaviors; food-seeking behavior (particularly for fat- and sugar-rich foods); specific food cravings.

10.2. Adrenal Insufficiency

At present, in developed countries, 80–90% of cases of primary adrenal insufficiency (AI) are caused by autoimmune adrenalitis, which may occur in isolation (40%) or as part of an autoimmune polyendocrinopathy syndrome (60%) [444]. Accordingly, autoimmune Addison disease is characterized by immune-mediated destruction of the adrenal cortex, and antibodies against

steroid 21-hydroxylase are detected in approximately 85% of patients with idiopathic primary AI, but only rarely in those with other causes of AI [444].

By contrast, this was not always the case: during the first half of the 20th century, tuberculosis was the most common cause of primary AI [444,445]. Moreover, this historical pattern still persists in many parts of the world: in developing countries, tuberculosis, disseminated fungal infections, and HIV remain significant causes of primary AI [398].

AI is a rare but potentially life-threatening endocrine disorder characterized by inadequate production of steroid hormones by the adrenal cortex—particularly cortisol and aldosterone as mentioned above—resulting in impaired metabolic homeostasis (e.g., reduced cortisol-driven gluconeogenesis), disturbances in fluid and electrolyte balance (especially involving sodium and potassium), and a deficient physiological response to stress [398,446,447]. The hyponatremia may be exacerbated by hypotension-induced ADH secretion and consequent water retention [446]. Clinical manifestations are often nonspecific and include fatigue (50%–95%), nausea and vomiting (20%–62%), and anorexia with WL (43%–73%) [448,449]. Despite the paucity of research on the mechanisms underlying nausea and vomiting in AI, it is well established that these signs and symptoms respond to GC replacement [450].

In rats, GC deficiency increases the anorexigenic CRH and suppresses the orexigenic NPY, a mechanism that may contribute to the anorexia and wasting seen in AI [415]. Nonetheless, patients with AI may appear to have a normal appetite, yet reach satiety after minimal food intake [451]. Importantly, some studies suggest that patients with idiopathic gastroparesis may have an increased likelihood of AI, highlighting the need for heightened clinical suspicion, although the exact prevalence of AI in this population remains unknown [452].

Aldosterone insufficiency typically manifests with lethargy, muscle cramps, postural hypotension, and salt craving, which may occur even in the absence of overt volume depletion owing to a voluntarily high-salt diet [453,454]. Sodium insufficiency is signaled to the brain through activation of central sodium-sensing mechanisms, osmoreceptors, and cardiac baroreceptors, as well as by elevated circulating levels of angiotensin II—a linear octapeptide hormone—and of aldosterone and corticosterone, the latter being the cortisol equivalent in rodents [455,456,457]. The specialized literature consistently underscores salt craving as a hallmark manifestation of AI [453,458,459,460,461,462,463,464]. Although this symptom may not always be evident at the initial clinical presentation, it possesses considerable diagnostic value [464,465]. Salt craving appears relatively specific to AI, being reported in approximately 15–20% of cases [458,466]. Some patients "chase" salt intake with lemon juice, whereas others consume remarkably large quantities of salt [460]. Additional reports describe a marked preference for salty foods such as peanuts, chips, and liquorice [462].

Whereas traditional presentations of AI typically include WL, contemporary patients may present as overweight or OB, sometimes owing to conditions such as early-onset obesity associated with AI and red hair, or as a late-stage manifestation of the disease [467].

Eating Behavior Profile: salt craving—the hallmark manifestation; nausea, vomiting, and anorexia within a wasting syndrome; early satiety associated with delayed gastric emptying (gastroparesis).

10.3. Conn Syndrome

Conn syndrome was first described by Jerome W. Conn (1907–1994) in 1955, when he published the inaugural report on primary aldosteronism (PA) in the medical literature [69,70,468,469,470,471].

Physiologically, aldosterone promotes sodium reabsorption and potassium excretion, primarily in the kidneys [471]. Although cortisol can exert mineralocorticoid effects, the enzyme 11β-hydroxysteroid dehydrogenase type 2 inactivates cortisol to cortisone, thereby permitting aldosterone to serve as the principal ligand of the mineralocorticoid receptor [471].

PA is defined by at least partially autonomous aldosterone production and represents the most common cause of secondary hypertension [470]. Its pathophysiology involves dysregulated aldosterone secretion that is independent of renin and not fully suppressed by volume or sodium loading, often occurring despite hypokalemia [471].

Obesity-related hypertension (ORH) is a multifactorial, polygenic condition. Multiple pathogenic mechanisms likely contribute to its development in people with OB, including hyperinsulinemia, activation of the renin–angiotensin–aldosterone system, sympathetic nervous system stimulation, and altered levels of adipokines (for example, leptin) or cytokines acting on the vascular endothelium [472].

Bansal et al. summarized several lines of evidence linking OB with PA [473]. Higher serum aldosterone concentrations and urinary aldosterone excretion have been observed in patients with increased BMI or larger waist circumference. In vitro and preclinical studies indicate that adipocytes can both synthesize and secrete aldosterone and release factors that stimulate aldosterone production by the adrenal glands. Aldosterone excess, producing ligand-dependent activation of the mineralocorticoid receptor, has been increasingly recognized as an important mechanism underlying ORH. This aldosterone excess may be conceptualized as acquired hyperaldosteronism, distinguishing it from the traditional, non-obesity-related presentations of PA. A recent meta-analysis reported a higher prevalence of MS among overweight or OB patients with PA [474].

A complex behavioral dimension of eating alterations in PA involves food preferences and habitual dietary patterns. Because food preferences play a key role in shaping eating habits, this aspect has particular clinical relevance [475]. In this context, hyperaldosteronism syndromes may promote a preference for a high-salt diet. Supporting this observation, some patients with PA report sodium cravings and consume excessive amounts of salt, thereby creating a convergence of factors that promotes the development of hypertension and its associated complications, including treatment-resistant hypertension, increased target-organ damage, and higher mortality [476].

Other eating-behavior-related aspects involving potassium and fructose in PA are more fragmented in the medical literature and remain less well defined.

Eating Behavior Profile: increased preference for high-salt foods; salt craving.

10.4. Pheochromocytoma

Adrenal pheochromocytoma (PHEO) is a tumor arising from catecholamine-producing chromaffin cells of the adrenal medulla that almost invariably produce, store, release, and metabolize catecholamines—dopamine, norepinephrine (noradrenaline), and epinephrine (adrenaline)—leading to potentially life-threatening systemic effects such as stroke, myocardial infarction, and multiple organ failure [477].

PHEO was first described at autopsy by Felix Fraenkel in 1886 [70,478]. Despite being an uncommon but treatable cause of hypertension, it has remained a challenge to clinicians [479].

The role of catecholamines in the regulation of FB and BW is complex and remains incompletely understood. Epinephrine (EPN) can stimulate FI under certain conditions, particularly when injected into specific brain regions or released in response to chronic stress [480]. However, in other scenarios, such as systemic administration or during acute stress, EPN can suppress appetite [481,482].

As described by Thomas et al., beyond these feeding-specific effects, EPN and norepinephrine, the primary effectors of the sympathetic nervous system and adrenal medulla, respectively, regulate adiposity and energy balance through multiple mechanisms [483]. They promote catabolism of triglycerides and glycogen, stimulate FI in the CNS, activate thermogenesis in brown adipose tissue (BAT), and modulate heat loss via peripheral vasoconstriction and piloerection. Thermogenesis in BAT is induced by cold exposure and overfeeding, and an inverse relationship exists between diet-induced thermogenesis and OB in both humans and animal models.

In addition to these thermogenic and feeding effects, physiologically, EPN, together with glucagon, GH, and T_3, constitutes a counter-regulatory hormonal response that prevents hypoglycemia by stimulating hepatic glucose production and limiting peripheral glucose uptake, thereby influencing FB through CNS signals that restore energy balance.

The understanding of the effects of feeding-related polypeptides on dopaminergic neurons remains incomplete. The ventral tegmental area (VTA), a key hub for reward-seeking behavior, is central to this modulation. In the VTA, pathological hyperinsulinemia disrupts insulin signaling and can increase feeding [484]. Leptin inhibits dopaminergic neurons projecting to the ventral striatum in rodents [485]. By contrast, ghrelin activates the mesolimbic dopamine system via nitric-oxide–associated mechanisms within the VTA [486].

DE in PHEO is generally linked to excess catecholamine secretion, which induces a hypermetabolic state and leads to WL—often despite normal appetite and FI (see discussion below) [487]. Nonetheless, anxiety can markedly suppress appetite [488]. Patients may also experience early satiety, nausea, vomiting, and abdominal pain due to the mass effect of the tumor [488,489] [490,491,492]. Although many symptoms improve or resolve after tumor removal, supportive care—including dietary management and strategies to address anxiety—remains important.

WL is a common manifestation of PHEO and reflects catecholamine-induced hypermetabolism [493,494]. Cachexia is a rarer manifestation [495]. In AT, catecholamines acting on β1-adrenergic receptors stimulate hormone-sensitive lipase, mobilizing stored triglycerides into free fatty acids and glycerol [496]. Concurrently, α2-adrenergic signaling suppresses pancreatic insulin secretion, blunting a major lipogenic drive—insulin normally promotes lipid storage, in part by stimulating LPL activity [496].

Elevated catecholamines also increase IR and decrease insulin secretion through the above-mentioned α2-adrenergic receptors, resulting in reduced glucose uptake as well as increased gluconeogenesis and glycogenolysis; 15%–35% of patients with PHEO present with impaired glucose tolerance or DM [497].

GI symptoms can also contribute to WL in PHEO, including nausea, vomiting, abdominal pain, and occasionally constipation or diarrhea [498].

Eating Behavior Profile: reduced appetite; early satiety; nausea, vomiting, abdominal pain, and diarrhea.

11. Growth Hormone Imbalances

The hypothalamic–pituitary–growth hormone (GH) axis is illustrated in Figure 1. The regulation of pulsatile GH secretion begins in the hypothalamus, located at the base of the third ventricle in the diencephalon, with the release of growth hormone–releasing hormone (GHRH, a 44-amino-acid peptide) from the arcuate nucleus and somatostatin (a 14-amino-acid peptide) from the periventricular nucleus (PeVN) [499,500,501,502]. GH, a glycoprotein composed of 694 amino-acid residues, is secreted by somatotrophs in the anterior pituitary and promotes anabolism and growth in multiple tissues, both directly and indirectly through insulin-like growth factor 1 (IGF-1, a 70-amino-acid polypeptide), which is primarily produced by the liver [499,503,504]. In AT, however, GH exerts catabolic effects by stimulating lipolysis (via activation of hormone-sensitive lipase) and promoting the release of free fatty acids and glycerol to support lipid metabolism [499,505]. GH, IGF-1, and free fatty acids all inhibit GH release, either directly at the pituitary or indirectly by stimulating somatostatin release from the PeVN [499].

Thus, the traditional effects of GH include stimulation of cell proliferation, tissue and body growth, the previously described lipolysis, and IR [506]. Beyond these peripheral actions, as outlined by Egecioglu et al., GH also acts in the CNS, where it influences FB and well-being in humans [507]. Experimental evidence in rodents further supports this role, showing that GH increases FI and alters feeding patterns. Consistent with these behavioral effects, both human and rat brains express GH and its receptor in the hypothalamus, hippocampus, and amygdala—regions

that regulate feeding, energy balance, and motivation—highlighting a central role in feeding control.

In humans, disruption of the hypothalamic–pituitary–GH axis may result either from GH overproduction and downstream hormonal excess—most often due to pituitary tumors in conditions such as pituitary gigantism (before epiphyseal fusion of the long bones) or acromegaly (after epiphyseal fusion)—or from congenital or acquired GH deficiency, as discussed below [499].

11.1. Gigantism

Pituitary gigantism is a rare condition caused by chronic hypersecretion of GH and IGF-1 due to a pituitary somatotroph adenoma [508]. Clinically, in addition to accelerated linear growth before epiphyseal closure, case reports and reviews from the twentieth century to the present consistently describe increased—sometimes voracious—appetite and WG, including OB, in affected patients [508,509,510,511,512,513,514,515].

Of importance, X-linked acrogigantism (X-LAG) is a recently described syndrome of pituitary gigantism caused by microduplications on chromosome Xq26.3 that encompass the gene *GPR101*, which is highly upregulated in pituitary tumors. Notably, 7 of 18 patients (38.9%) present with a prior history of increased appetite—or especially other food-seeking behaviors—a feature uncommon in other forms of gigantism [516].

GH is an insulin counter-regulatory hormone (see Subsection 10.4) with profound metabolic consequences for the body. Its actions help explain the development of IR, hyperinsulinism, and the resulting glycemic disturbances, as well as the striking clinical manifestation of acanthosis nigricans—observed in 22.2% of patients with X-LAG—often appearing in the flexural regions of individuals affected by gigantism [516,517].

Eating Behavior Profile: increased—sometimes voracious—appetite; food-seeking behavior, as seen in X-linked acrogigantism.

11.2. Acromegaly

A recent study applied the Hedonic Hunger Scale (HHS), assessed using the Dutch Eating Behavior Questionnaire (DEBQ), to evaluate hedonic hunger—defined as eating for pleasure—and its effects on EBs in patients with acromegaly (ACRO) due to excess GH (n = 55), compared with individuals with non-functional pituitary adenomas (n = 39) and healthy controls without pituitary disease (n = 34) [518,519]. The median ages of patients with ACRO and non-functional adenomas were 53 and 54 years, respectively, while the control group was age-matched (median 53 years) [518]. In addition, participants completed the Hospital Anxiety and Depression Scale (HADS) through face-to-face interviews to evaluate psychiatric comorbidities [518]. Results showed that average total scores and median values of emotional and external eating on the HHS (DEBQ) were significantly higher in the control group than in the ACRO group. Conversely, in the HADS, the depression subscale score was significantly higher in patients with ACRO compared to those with non-functional adenomas.

According to the DSM-V, individuals with atypical depression are generally more prone to WG and OB than those with typical (melancholic) depression [520].

Although ACRO is associated with an increased risk of psychiatric disorders, including depression, current research does not consistently indicate that atypical depression is more frequent than other forms of depression in patients with ACRO [521,522]. Some studies, however, suggest that chronic depression—which may include features of atypical depression—is relatively common in these patients and can sometimes precede the diagnosis of pituitary pathology [523]. Excessive GH secretion and the associated hormonal disturbances in ACRO likely contribute to the psychological burden, including the development of depressive symptoms, although this relationship requires further investigation [521,524].

OB is common in ACRO, with over 40% of patients exhibiting a body mass index (BMI) greater than 30 kg/m², reflecting a high prevalence of overweight and OB [525]. This prevalence correlates positively with disease activity, such that higher IGF-1 levels are associated with higher BMI [526]. Although excess GH and IGF-1 often reduce visceral and subcutaneous fat, they simultaneously increase intermuscular fat, contributing to IR and elevated OB risk [527]. Furthermore, ACRO is linked to a markedly increased risk of cardiovascular complications—including arrhythmias and cardiomyopathy—which are major contributors to morbidity and mortality in these patients [528].

Eating Behavior Profile: appetite and other eating behaviors usually preserved.

11.3. Growth Hormone Deficiency

Children with GH deficiency exhibit reduced growth velocity, which typically becomes evident toward the end of the first year of life [529]. At this stage, the hormone-dependent phase of childhood growth fails to replace the nutrition-dependent phase of infancy [529]. Consequently, affected children may develop truncal OB, a facial appearance that seems younger than their chronological age, and crowding of the facial features toward the midline, suggestive of maxillary hypoplasia [529]. In such cases, the primary goal of GH replacement therapy is to restore growth velocity and enable the attainment of adult height within both the normal range and the individual's target height range (i.e., genetic potential) [530].

According to Wass and Sönksen, in adults with GH deficiency, lean body mass is reduced by approximately 8% (≈4 kg of lean tissue); however, this deficit can be fully reversed after six months of GH replacement therapy [531]. Conversely, body fat is typically increased and distributed more centrally (abdominally) than peripherally. A mean reduction of 5 kg in body fat during the first month of GH replacement therapy has been reported, particularly at central sites [531].

GH deficiency is rare but may occur in secondary forms—for example, in neurosarcoidosis, which frequently localizes to the basal brain and may damage hypothalamic centers [532,533]. Such involvement can lead to disturbances in consciousness, body temperature regulation, vascular control, thirst, appetite, and FB [533].

Reported manifestations include diabetes insipidus (37.3%), polydipsia (31.9%), changes in smell, taste, and hearing (5.5%), OB or WG (5.5%), hypothermia (4.4%), anorexia (4.4%), growth impairment (3.3%), hypodipsia (2.2%), hyperphagia (2.2%), and nausea (1.1%) [533].

To conclude, it is worth highlighting ghrelin, a potent orexigenic hormone that not only stimulates appetite but also activates GHRH-containing neurons in the arcuate nucleus of the hypothalamus [534]. This dual action suggests a complex interplay with leptin in linking the gut, energy homeostasis, and the neuroendocrine regulation of both GH and gonadotropins [535]. Despite this central role, circulating ghrelin levels appear to be comparable in ACRO and GH deficiency and, to date, do not seem to contribute meaningfully to the weight and eating disturbances discussed here [536,537].

Eating Behavior Profile: sensory changes (smell, taste), anorexia or hyperphagia; nausea, as seen in neurosarcoidosis.

12. Conclusion

In daily clinical practice—based on personal experience, particularly in Manaus (population ≈2,063,689), Brazil—eating and weight disturbances associated with endocrine diseases are most commonly observed in patients with T2DM, followed by thyroid dysfunction and, less frequently, by CS secondary to long-term corticosteroid therapy (iatrogenic CS).

In T2DM, once adequate treatment is initiated, symptoms and metabolic disturbances progressively improve as glycemic variability decreases and near-normoglycemia is reestablished. The earliest symptoms to resolve are typically those of the traditional triad—polyuria, polydipsia, and polyphagia. At this stage, modest WG is common, reflecting metabolic rebalancing as glycosuria subsides and insulin-mediated anabolism is restored.

In thyroid dysfunction, initiation of antithyroid therapy for hyperthyroidism—typically combined with β-blockers—reduces adrenergic activity, particularly tachycardia, until euthyroidism is achieved. In hypothyroidism, restoration of physiological function requires gradual initiation of hormone replacement therapy, largely because the positive inotropic effects of THs can significantly impact cardiac function, especially in the elderly.

In CS, tapering corticosteroid therapy attenuates many manifestations in both behavioral (e.g., improved mood and emotional stability) and biological domains (e.g., reduced IR and improved glycemic control), resulting in overall clinical improvement. However, centripetal redistribution of body fat—namely, COB characterized by fat accumulation in the trunk and abdomen—tends to be more resistant to reversal, owing to factors such as abdominal adipocyte hypertrophy and increased LPL activity [538].

By contrast, public health centers in the world's more densely populated and cosmopolitan cities diagnose and manage a greater number of rare endocrine disorders, largely owing to a higher concentration of specialists, advanced diagnostic infrastructure, and well-established referral networks.

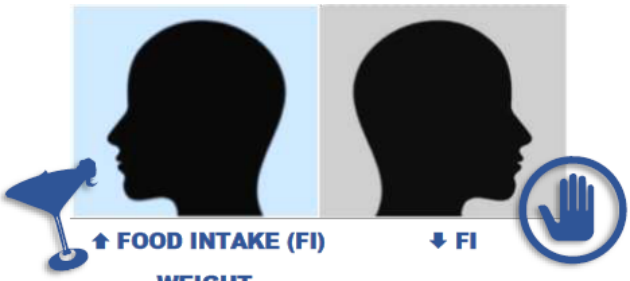
Figure 7 provides an overview of the alterations in EB and BW associated with the endocrine disorders examined in this work, highlighting notable contradictions.

Nevertheless, the natural history of most endocrine disorders discussed here generally reflects a coherent relationship between FI and BW. Hypothalamic syndromes—particularly PWS—exhibit a clear pathophysiological substrate, namely permanently elevated ghrelin. Other examples include pituitary cachexia; chronic complications of DM, such as gastroparesis with WL and neuropathic diabetic cachexia; and insulinoma, which may lead to hypoglycemia and OB. Disorders of the HPO axis, such as PCOS, are associated with WG or OB. Adrenal diseases show distinct patterns: CS and Conn syndrome often result in COB, whereas PHEO can cause WL. GH imbalances also influence both FI and BW, as seen in gigantism, acromegaly, and GH deficiency. Collectively, these examples highlight the pathophysiologically coherent ways in which endocrine disorders shape EB and BW, underscoring the intricate links between hormonal regulation and energy balance.

However, some endocrine disorders exhibit a seemingly paradoxical relationship between EB and resulting BW. A clear example is thyrotoxicosis with hyperthyroidism, where increased calorigenesis—partly due to the uncoupling of oxidation from phosphorylation, with the uncaptured energy dissipated as heat [539]—prevents WG despite hyperphagia. The hypercatabolic effects of excess T_3 counterbalance the increased energy intake, causing rapid WL. In contrast, the situation in hypothyroidism is less contradictory: T_3 deficiency reduces FI, leading to anorexia, which is consistent with the ongoing hypometabolism, while the modest WG observed is largely due to reduced suppression of hyaluronic acid production and the consequent water retention.

Finally, as discussed in this review, parathyroid disorders are associated with diverse alterations in EB and BW that are only beginning to be understood. Accordingly, careful attention should be given to the emergence of potentially deleterious DE conditions, such as diabulimia. This dynamic area, integrating EB and BW, continues to challenge researchers as the concept of food noise (FN) gains complexity in discussions of OB, weight management, and eating disorders. FN may be defined as persistent thoughts about food that are perceived by the individual as unwanted and/or dysphoric and that may cause harm, including social, mental, or physical problems [540].

Alterations in EB and BW in endocrine disorders arise directly from their underlying pathophysiology, underscoring the need for a thorough, mechanistically specific understanding—an objective pursued in the present work. Knowledge of EB and BW regulation, more broadly, however, is inherently multidisciplinary and should be approached from a broad, integrative perspective.



⬆ FOOD INTAKE (FI)	⬇ FI
WEIGHT VARIATION (WV)	WV
HS (e.g., PWS) OB	Pituitary CACHEXIA
Hyperthyroidism, WL (*)	Hypothyroidism, WG (*)
	PHPT, WL, OB (*)
	SHPT, WL, OB (*)
	HypoPT, WL, OB (*)
T2DM, WG, OB	T1DM, DIABULIMIA, NW, WG
Insulinoma, WL, OB (*)	DMG, WL, DN CACHEXIA
PMS, NW, WG, CRC, WG, PCOS, OB	
CS, SOB, AI, WL, OB (*)	PA, OB PHEO, WL
Gigantism, OB, ACRO, NW, OB (*)	GH deficiency, OB (*)

⬆: increased; ⬇: decreased; **FI**: food intake; **WV**: weight variation; **HS:** hypothalamic syndrome; **PWS**: Prader-Willi syndrome; **OB**: obesity; **WL**: weight loss; **WG**: weight gain; **NW**: normal weight; **PHPT**: primary hyperparathyroidism; **SHPT**: secondary hyperparathyroidism; **HypoPT**: hypoparathyroidism; **T2DM**: type 2 diabetes mellitus; **T1DM**: type 1 diabetes mellitus; **DMG**: diabetes mellitus gastroparesis; **DN cachexia**: diabetic neuropathic cachexia; **PMS**: premenstrual syndrome; **CRC**: contraceptive-related changes; **PCOS**: polycystic ovary syndrome; **CS**: Cushing syndrome; **AI**: adrenal insufficiency; **PA**: primary aldosteronism; **PHEO**: pheochromocytoma; **ACRO**: acromegaly; **GH deficiency:** growth hormone deficiency.

Note. This illustration depicts a complex, seemingly paradoxical clinical scenario. In other words, changes in EB do not always translate into the expected changes in BW in endocrine disorders (e.g., excessive FI leading to WG), thereby revealing a dissociation between appetite and weight regulation. For example, as noted in Subsection 8.3, WG is more common in insulinoma; however, WL may occur when patients restrict FI to control symptoms or when the tumor is malignant. Thus, this phenomenon reflects, at least in part, the multiplicity of underlying mechanisms.

Figure 7. Diagram of the dissociation between eating behavior and body-weight alterations in endocrine disorders (asterisked disorders in particular)

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Conflict of Interest

The author declares no conflict of interest.

List of Abbreviations:

AAs: amino acids;
ACh: acetylcholine;
AChRs: acetylcholine receptors;
ACRO: acromegaly;
ACTH: adrenocorticotropic hormone;
AD: Alzheimer disease;
ADH: antidiuretic hormone;
AgRP: agouti-related peptide;
AI: adrenal insufficiency;
Ala: L-alanine;
AP: anterior pituitary;
Arg: L-arginine;
AT: adipose tissue;
BAT: brown adipose tissue;
BBB: blood–brain barrier;
BMI: body mass index; **BW**: body weight; body-weight (attributive form);
Ca: calcium; **CART**: cocaine- and amphetamine-regulated transcript;
CaSR: calcium-sensing receptor;
CCK: cholecystokinin;
CD: Cushing disease;
CKD: chronic kidney disease;
CNS: central nervous system;
COB: central obesity;
CRC: contraceptive-related changes;
CRH: corticotropin-releasing hormone;
CS: Cushing syndrome;
DA: dopamine (prolactin-inhibiting hormone);
DE: disordered eating/disordered-eating (attributive form);
DEBQ: Dutch Eating Behavior Questionnaire;
DG: diabetic gastroparesis;
DKA: diabetic ketoacidosis;
DM: diabetes mellitus;
DNC: diabetic neuropathic cachexia;
DSM-5: *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition;
E/Es: estrogen/estrogens;
E_1: estrone;
E_2: estradiol;
E_3: estriol;
E_4: estetrol;

EB/EBs: eating behavior/eating behaviors;
EE: energy expenditure;
EPN: epinephrine;
FATP: fatty acid transport protein;
FB/FBs: feeding behavior/feeding behaviors;
FI: food intake;
FN: food noise;
FSH: follicle-stimulating hormone;
GABA: gamma-aminobutyric acid;
GC/GCs: glucocorticoid/glucocorticoids;
GH: growth hormone;
GHRH: growth hormone-releasing hormone;
GI: gastrointestinal;
GIP: glucose-dependent insulinotropic polypeptide (formerly gastric inhibitory polypeptide);
GIPR: glucose-dependent insulinotropic polypeptide receptor;
Gln: L-glutamine;
GLP-1: glucagon-like peptide-1;
GLP-1R: GLP-1 receptor;
GLUTs: glucose transporters;
GnRH: gonadotropin-releasing hormone;
GRP: gastrin-releasing peptide;
HADS: Hospital Anxiety and Depression Scale;
HHS: Hedonic Hunger Scale;
HPA: hypothalamic–pituitary–adrenal axis;
HPO: hypothalamic–pituitary–ovarian axis;
HPT: hypothalamic–pituitary–thyroid axis;
HS: hypothalamic syndrome;
HypoPT: hypoparathyrodism;
ICD-11: *International Classification of Diseases*, 11th revision;
IGF-1: insulin-like growth factor 1;
Ile: L-isoleucine;
IR: insulin resistance;
KBs: ketone bodies;
Leu: L-leucine;
LH: luteinizing hormone;
LPL: lipoprotein lipase;
M3Rs: muscarinic acetylcholine receptors;
MS: metabolic syndrome;
NPY: neuropeptide Y;
NW: normal weight/normal-weight (attributive form);
OB: obesity;
ORH: obesity-related hypertension;
OT: oxytocin;
P: progesterone;
PA: primary aldosteronism;
PCOS: polycystic ovary syndrome;
PD: Parkinson disease;
PeVN: periventricular nucleus;
PHEO: pheochromocytoma;
PHN: paraventricular hypothalamic nucleus;
PHPT: primary hyperparathyroidism;
PMS: premenstrual syndrome;
PNS: peripheral nervous system;
POMC: proopiomelanocortin;
PRL: prolactin;
PTH: parathyroid hormone;
PWS: Prader–Willi syndrome;
Refs: references;
SAB: sympathetic autonomic branch;
SHPT: secondary hyperparathyroidism;
SOB: sarcopenic obesity;
T1DM: type 1 diabetes mellitus;
T2DM: type 2 diabetes mellitus;
T_3: triiodothyronine (active hormone);
T_4: tetraiodothyronine or thyroxine (prohormone);
TH/THs: thyroid hormone/thyroid hormones;
TNF-α: tumor necrosis factor-alpha;
TRH: thyrotropin-releasing hormone;
TSH: thyroid-stimulating hormone;
VTA: ventral tegmental area;
WG: weight gain;
WL: weight loss/weight-loss (attributive form);
WV: weight variation;
X-LAG: X-linked acrogigantism.

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