CHAPTER 32

THERAPEUTIC STRATEGIES OF ENDOCRINE AND METABOLIC DISORDERS

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INTRODUCTION

The endocrine system comprises of glands secreting different hormones directly into the blood stream. Basically the hormones reach almost every cell and this communication is slower than the nerve communication, but is more persistent. Other than endocrine glands, additional sources of hormones are also present in the body such as prostaglandins are produced and secreted from plasma membranous phospholipids of many cells. Some prostaglandins are responsible for causing pain and inflammation, especially in case of arthritis, while some others show their actions with pituitary hormone oxytocin to cause uterine contractions during childbirth. Some organs produce specific hormones such as intestine (cholecystokinin, secretin, and gastrin), liver (hepcidin, insulin-like growth factor, and thrombopoetin), kidney (angiotensin, renin, and erythropoietin) and even the heart (atrial natriuretic peptide). The major endocrine glands, including the pituitary, thyroid and parathyroid glands, pancreas, adrenal glands and the reproductive organs (ovaries and testes) are represented in Figure 1. All the endocrine glands are interconnected with one another and secrete different hormones for regulation of homeostasis, growth and development, and metabolism and reproduction in the body by direct transmitting messages to the target organ receptors. To keep the balance in hormonal levels, complex feedback system is present, working in form of positive and negative feedback mechanisms to control the secretion of hormones (Shier et al. 2007).

The pituitary gland is a pea-sized endocrine gland, also referred to as 'master gland' of the body because in addition to secret its hormones, it controls other body glands to secrete hormones. Another name for pituitary is hypophysis (Greek word for 'lying under') that indicates its location just on the underside of the brain. Pituitary gland has two main parts; the anterior (front) and the posterior (back) lobe. Pituitary stalk connects hypothalamus and pituitary via blood vessels and nerves. Hypothalamus communicates with anterior lobe of pituitary through hormones and posterior lobe of pituitary through nerve fibers. The hypothalamus is the region of brain located below the thalamus and above the pituitary and contains a control center for autonomic (heart rate, blood pressure, body temperature, digestion) and endocrine (release of pituitary hormones via hormone releasing factors) functions of the pituitary because of its complex interactions. Thus, hypothalamus is the prime link connecting the nervous system and the endocrine system (Guyton 1981).

The thyroid gland is a butterfly-shaped gland located on either side of the trachea. It is comprised of follicular and less numerous parafollicular cells (C cells), secreting the thyroid hormones including triiodothyronine (T3), thyroxin (T4) and calcitonin. These hormones affect different body organs and tissues like adipose tissue, musculoskeletal system and the heart. From hypothalamus, thyrotropin releasing hormone (TRH) is released and is responsible for the secretion of thyroid stimulating hormone (TSH) from anterior pituitary, which ultimately stimulates the thyroid to release T3 and T4 to affect other tissues. These hormones also inhibit the release of TRH from hypothalamus through feedback mechanism. Other factors can also inhibit TSH secretion including glucocorticoids, stress and warmth. Calcitonin secreting from parafollicular cells regulates body calcium levels depending on serum calcium rather than feedback mechanism. Just posterior to thyroid glands, the parathyroid glands are located. These glands are comprised of three types of cells with different functions. Parathyroid hormone (PTH) is produced and secreted by chief cells of parathyroid glands. This hormone causes active vitamin D production from kidneys, stimulates calcium reabsorption and inhibits phosphate reabsorption from renal tubules. In addition, PTH releases calcium from bones in response to low serum calcium concentration, while an increased calcium concentration prevents the production and release of PTH. Adrenal glands are the triangular shaped glands located at the apex of both kidneys. The outer surface (cortex) of gland secretes mineralocorticoids (aldosterone), glucocorticoids (cortisol) and additional sex hormones. The inner portion (medulla) of gland secretes adrenaline and noradrenaline. Corticotropin releasing factor (CRF) from hypothalamus stimulates pituitary to release adrenocorticotropic hormone (ACTH) and melanocyte stimulating hormone (MSH). The ACTH acts on adrenal glands

How to cite this chapter: Hussain Z, Khan JA, Rashid H, Noreen N, Siddique R, Mushtaq A, Kousar S and Rasheed MU, 2022. Therapeutic strategies of endocrine and metabolic disorders. In: Abbas RZ, Khan A, Liu P and Saleemi MK (eds), Animal Health Perspectives, Unique Scientific Publishers, Faisalabad, Pakistan, Vol. I, pp: 238-246. https://doi.org/10.47278/book.ahp/2022.32

to produce and release aldosterone and cortisol. When adequate concentration of cortisol and aldosterone is achieved, the hypothalamus stops producing ACTH and MSH. The pancreas is situated just behind the stomach in upper left abdomen and surrounded by the liver, spleen and the intestine (Werbel and Ober 1993). Pancreas is a heterocrine gland with 99% exocrine and 1% endocrine function. The endocrine portion of pancreas involves clusters of cells called islets of Langerhans that is comprised of alpha cells secreting glucagon, beta cells secreting insulin and delta cells secreting somatostatin hormones. Low glucose level in the serum stimulates glucagon release from pancreas to initiate glucose production via gluconeogenesis. Other factors can also trigger glucagon release such as trauma, exercise and some infection. Insulin is crucial for efficient metabolism and cellular utilization of glucose. Ovaries are the part of female reproductive system present on each side of the uterus, while testes are the part of male reproductive system present inside the scrotum. From hypothalamus, gonadotropin releasing hormone (GnRH) is released to act on pituitary to release follicle stimulating hormone (FSH) and luteinizing hormone (LH) which ultimately cause the release of estrogen and progesterone from the ovaries in women. In men, LH stimulates testes for testosterone production and release (Rhee 2021).

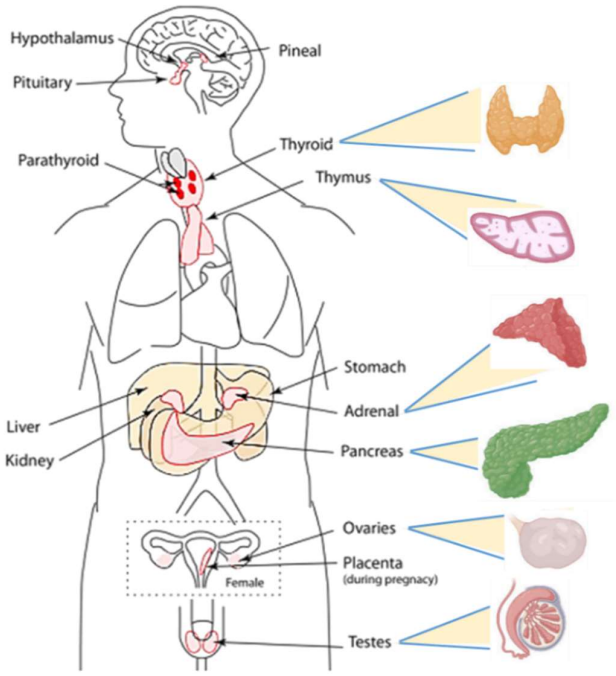

Figure 1: The endocrine system. Major endocrine glands include the hypothalamus, pituitary gland, thyroid and parathyroid gland, pancreas, adrenals, ovary, placenta and testis. Adapted from source: http://hyperphysics.phy-astr.gsu.edu/hbase/Biology/endocr.html

Endocrine and Metabolic Disorders

When body metabolic process fails to work properly in form of having too much or too little hormones or other essential substances for keeping healthy, a number of metabolic disorders arise. Hormonal alterations from endocrine glands result in metabolic syndrome. The major causes of metabolic syndrome are sedentary lifestyle, dietary habits, smoking and excess weight that may result in lethal consequences. Endocrine disorders extent enormous conditions and affect quality as well as quantity of life. Major endocrine disorders include hypopituitarism, acromegaly, diabetes insipidus and diabetes mellitus, hypogonadism, prolactinoma and Cushing's syndrome. Among endocrine disorders, thyroid diseases are more common (Goodman and Synder 2007).

Hypothalamus Deficiencies

The hypothalamus is a small portion of the brain located on the undersurface of brain and lies just below the thalamus and above the pituitary gland. It synthesizes hormones (releasing factors) and produces nerve impulses that regulate the secretion of pituitary gland. Hence, tumors of the hypothalamus or any other deficiency may directly affect pituitary hormones or can interfere with the appetite control center, causing obesity (Guyton 1981).

Pituitary Gland Related Acromegaly

Acromegaly is an uncommon systemic disorder affecting the whole body (Vance 2010) that arises as a result of excessive production and secretion of GH. Meanwhile GH regulates the overall growth of bones, muscles, internal organs and triggers the insulin-like growth factor 1 (IGF-1) secretion. In case of acromegaly, both GH and IGF-1 levels are increased, giving rise to metabolic alterations and tissue enlargement which eventually causes visible body malformations (Fleseriu et al. 2010). This disease generally occurs between the age of 30 and 50 with slow progression, actually delaying the diagnosis at later stages. Generally, GH neutralizes the insulin effects on glucose utilization and controls tissue reaction to insulin; therefore, excessive GH may result in insulin resistance. The patients suffering from acromegaly often experience higher levels of serum triglycerides demonstrating abnormal lipid metabolism associated with acromegaly (Colao et al. 2004).

Galactorrhea or Hyperprolactinemia

Galactorrhea is a lactating condition in non-breastfeeding women or in men, mostly caused by tumors of pituitary (prolactinoma or adenoma) secreting prolactin. In women, mostly the tumors are in form of microadenomas <10 mm in diameter, however in men, the frequency of these microadenomas is comparatively less. Lesions of pituitary gland can raise prolactin levels by constricting the pituitary stalk. This can decrease the actions of dopamine (prolactin inhibitor). Some medications, like antipsychotics (phenothiazine), antihypertensives (alpha-methyldopa) and opioids can also cause galactorrhea or hyperprolactinemia. Increased levels of thyroid releasing hormones increases the TSH and prolactin secretions, so, hyperthyroidism can be an important cause of hyperprolactinemia. It can be linked to hypogonadism due to GnRH deficiency acting on pituitary gonadotropins (Goodman and Synder 2007).

Erectile Dysfunction

Erectile dysfunction (ED) is an inability in men to have an erection hard enough to gain or maintain sexual satisfaction. It is the most common sex problem that almost every man irregularly meets an erection problem. In primary ED, the person is unable to erect or retain an erection, while in

secondary ED, the person was previously able to erect but in late age, develops ED. The latter is more common than former ED. In the USA, about 50% of men by age 40-70 are usually affected, however, ED is not necessarily occur with advanced age and can be treated at any age. For erection, the penis requires to have sufficient blood flow, the normal functioning nerves, enough libido (sexual desire) and the adequate amount of testosterone (male sex hormone) and hence any of the system's problems can be a reason for ED (Guyton 1981).

Central Diabetes Insipidus

Diabetes insipidus occurs as an outcome of deficiency of ADH (vasopressin) due to hypothalamic-pituitary disorder (central diabetes insipidus) or renal resistance to ADH (nephrotic diabetes insipidus), results in polyuria and polydipsia. ADH stimulates water preservation by enhancing the epithelial permeability of the renal tubules to water. At higher levels, this hormone causes vasoconstriction. Like aldosterone, vasopressin preserves cellular and vascular hydration as well as humoral homeostasis. The main stimuli for ADH secretion in the body are the volumetric consumption detected by vascular baroreceptors and an increased osmotic pressure of water detected by hypothalamic osmoreceptors. ADH is produced in the hypothalamus and stored in posterior pituitary. If hypothalamic nucleus and neurohypophysis region remain intact, the hormone is secreted into the circulation. Even 10% of intact neurosecretory neurons can avoid central diabetes insipidus as these neurons cover supraoptic and paraventricular nucleus of hypothalamus and pituitary stalk (Joshi et al. 2011).

Hypopituitarism

It is a rare disorder that prevails as an outcome of decreased secretion of one or more pituitary hormones. A number of factors may involve including inadequate blood supply to the pituitary, some inflammatory diseases, infections, autoimmune disorders, head injury, irradiation, and surgical removal of pituitary tissues or tumors of pituitary gland or hypothalamus (Guyton 1981).

Growth Hormone Deficiencies

Growth hormone (GH) deficiency results in overall short stature, also known as dwarfism especially in children. In adults, it might not usually affect height as the bones are completely developed and grown-up but they may lose energy (Enger et al. 2003).

Prolactin Deficiency

Prolactin deficiency reduces or stops the ability of women for breast milk production after childbirth. A rare birth complication known as Sheehan syndrome is the main cause of low prolactin concentrations and other hormones of pituitary. It usually develops due to shock and excessive loss of blood during delivery, partially damaging the pituitary. Deficiency of prolactin in men has no serious effects.

Gonadotropins (FSH and LH) Deficiency

Deficiencies of FSH and LH in women before menopause can cause cessation of menstrual cycle, infertility, vaginal dryness and loss of feminine sexual characteristics. In men, deficiency of these hormones leads to reduced sperm production, erectile dysfunction, testicular atrophy and loss of masculine sexual characteristics with secondary infertility, while in children this deficiency lead to delayed puberty.

Thyroid Gland Related Hyperthyroidism

Hyperactivity of thyroid gland is hyperthyroidism; also known as hypermetabolic state or thyrotoxicosis. Thyroid storm is uncommon but life-threatening disorder prevailing in 1–2% patients with hyperthyroidism. Thyroid storm occurs during excessive stress owing to adverse drug reactions, diabetic crisis or additional serious contests. The most common type of hyperthyroidism is Graves' disease; an autoimmune disorder followed by active secretion of excessive thyroid hormones due to TSH-mimicking antibodies. It commonly occurs in women during their middle-ages and can also affect men. A number of factors can cause hyperthyroidism such as high iodine-loaded drugs (iodinated IV substances or amiodarone), autoimmune destruction of thyroid gland or acute toxicity of thyroid hormones (exogenous), resulting in hypersecretion of thyroid hormones (Weetman 2000).

Hypothyroidism

Hypothyroidism is a condition of inadequate thyroid hormone secretions resulting in a decrease in overall body metabolism. Primary and secondary hypothyroidism are two major categories of hypothyroidism. Any deficiency in hormonal secretion or thyroid destruction can cause primary hypothyroidism. In the USA, Hashimoto's Thyroiditis is the leading cause of primary hypothyroidism. It is an autoimmune disorder characterized by thyroid cells being attacked by the body's immune system, resulting in destruction of thyroid cells. Secondary hypothyroidism results due to hypothalamic or pituitary disease leading to inadequate secretions of either thyroid hormones or thyroid stimulating hormone. Myxedema coma is a lethal condition of chronic hypothyroidism followed by severe hypotension, hypoglycemia, bradycardia and lower serum sodium levels (hyponatremia). Hypothyroidism is commonly caused by iodine deficiency. As iodine is critical for production and release of thyroid hormones, the disease manifests as congenital hypothyroidism since birth characterized by physical deformities, brain dysplasia and delayed growth. It can be treated by adequate iodine supplementation (Durante et al. 2018).

Parathyroid Gland Related Hypoparathyroidism

Hypoparathyroidism is a condition characterized by hypocalcemia, occurring as a result of insufficient levels of serum PTH or resistance to the effects of PTH. Besides, some congenital, acquired or autoimmune diseases can cause hypoparathyroidism. Resection of the gland during thyroidectomy or some injury lead to acquired hypoparathyroidism (Bilezikian 2020).

Adrenal Gland Related Acute Adrenal Insufficiency

In this condition, body needs more levels of mineralocorticoids and glucocorticoids than the normal capacity of adrenal glands. The major reason of such condition is the abrupt cessation of

steroid drugs following prolonged use. It may occur when the patient is unable to get the proper dose during stress, e.g., after major trauma, surgery or during a disease. Acute disease is categorized into primary, secondary and tertiary class depending on respective endocrine gland dysfunctioning. Primary adrenal insufficiency is associated with adrenal dysfunctioning, secondary adrenal insufficiency is associated with pituitary dysfunctioning, while tertiary adrenal insufficiency is related to the hypothalamic dysfunctioning (Werbel and Ober 1993).

Chronic Adrenal Insufficiency

Failure of adrenal cortex to secrete adequate levels of cortisol leads to chronic adrenal insufficiency. Like acute dysfunctioning, it is also categorized as primary, secondary and tertiary class depending upon either direct or indirect damage of the cortex. Primary adrenal insufficiency is commonly regarded as Addison's disease. It is both endocrine and metabolic disorder arise from direct injury to the adrenal cortex due to some autoimmune diseases, adrenal hemorrhage, tuberculosis, meningococcemia pathophysiology and acquired immunodeficiency syndrome (AIDS) (Arlt and Allolio 2003). It is a chronic illness with long-term attack. As known, adrenal cortex secretes aldosterone and cortisol. Aldosterone maintains a balance of sodium and potassium level in serum. Under stress conditions (heart ischemia, trauma, serious illness or infection), the adrenal glands become unable to secrete adequate level of corticosteroids (cortisol) to encounter body's need, exacerbating Addison's disease. In secondary class, the cortex is intact, but the pituitary becomes unable to secrete ACTH to stimulate the release of cortisol, so it is one step slighter than primary adrenal insufficiency. In the tertiary adrenal sufficiency, ACTH is not released from pituitary due to pituitary-hypothalamic disease (Hahner et al. 2010). Hyperpigmentation owing to excessive MSH production is the key distinctive feature of primary adrenal insufficiency, because ACTH and MSH are secreted from solitary pro-hormone peptide precursor pro-opiomelanocortin. MSH stimulates melanocytes to produce melanin. Both secondary and tertiary adrenal insufficiency are related to lower MSH levels, thus cannot be associated with hyperpigmentation (Arlt and Allolio 2003).

Hyperadrenalism (Cushing's syndrome)

Hyperadrenalism refers to as Cushing's syndrome and may occur due to overproduction or excessive exposure of serum cortisol from adrenal cortex. It commonly occurs among women of age 20-50 years. It may occur due to prolonged use of corticosteroids or pituitary or adrenal tumors. Regardless of the cause, increased levels of cortisol can lead to the interruption in normal metabolism of lipids, proteins and carbohydrates which may result in muscle weakness, fragile bones and hyperglycemia (Thomas et al. 1984).

Pancreas Related Diabetes Mellitus

Diabetes is one of the most prevalent endocrine disorders characterized by a number of combined ailments recognized by high blood sugar levels or hyperglycemia (Joshi et al. 2011). Diabetes is a metabolic syndrome characterized by lack of balance in insulin synthesis and action. Insulin plays crucial role in the absorption and cellular utilization of glucose (Taxitiemuer et al. 2011). Beta cells dysfunctioning leads to deficient production of insulin and amylin eventually causing obesity. Hepatocyte nuclear factor 4-alpha from liver plays role in gene transcription of pancreatic beta cells. In type 2 diabetes, about 2-5% of beta cells are non-functional, gene mutations in liver may progress to maturity-onset diabetes of young people, and still it is noninsulin-dependent diabetes. Diabetic ketoacidosis (DKA) is an acute endocrine disorder characterized by plasma glucose concentration >350 mg/dL (>19.4 mmol/L), serum bicarbonate levels <15 mEq, ketone production and metabolic acidosis which is a clinical symbol of DKA. Its mortality rate is about 14%. In this condition, insulin deficiency and increased levels of glucagon lead to volumetric depletion, hyperglycemia as well as acidosis due to electrolyte imbalance. It is mostly caused by infections, myocardial infarction, trauma or pregnancy. Gestational diabetes occurs during pregnancy and even newborn is at greater risk. Clinically, diabetes is described by hyperglycemia and imbalances in lipid metabolism. For differential diagnosis, the threshold values for fasting blood glucose and random blood glucose are ~140 mg/dL (~7.7 mmol/L) and ~200 mg/dL (~11.1 mmol/L) respectively. Glycosylated hemoglobin's % age (glycated hemoglobin or HbA1c) is an indicator of controlled diabetes in patients within 3 months. Body's inability to control serum glucose levels may give rise to microvascular complications in the eyes, kidneys, nervous system and the heart (Pe et al. 2003; Kousar et al. 2021).

Hypoglycemia

A very common disorder related to diabetes is hypoglycemia in which blood glucose level is <60 mg/dL (3.3 mmol/L) and can vary person to person. At this stage, the body reduces insulin secretion to avoid sudden hypoglycemia. Meanwhile, there is more release of counter-regulatory hormones like adrenaline and noradrenaline and at last, cognitive degeneration occurs. There are substantial mental state alterations as the glucose level falls below 50 mg/dL (2.8 mmol/L). If untreated, morbidity and mortality increases. To avoid this, proper diagnosis and effective therapy are required. Hypoglycemia usually occurs as a result of high dose of insulin, reduced eating or both. Tissues of central nervous system differ from other ones in their way of metabolizing proteins, fats and sugar, especially they depend entirely on glucose as the source of energy. If blood glucose levels drop abruptly, the brain becomes starved. In patients without history of diabetes, hypoglycemia is regarded as postprandial or fasting hypoglycemia and is reflected by hyperinsulinemia, often observed in patients undertaking gastric surgery. Hypoglycemia can be triggered by pancreatic tumors or insulinoma, enzyme deficiency, liver disease, infections and drug overdose (sulfonylureas, insulin) (Pe et al. 2003).

Therapeutic Strategies

Pharmacological Interventions in Combating Endocrine and Metabolic Disorders

Endocrine and metabolic disorders can be caused by a number of risk factors including chronic inflammation, glucose intolerance or oxidative stress causing mitochondrial dysfunctions, shifting natural balance of endocrine and

metabolic system towards disordered state, as shown in Figure 2. The recent guidelines for treatment and management of metabolic and endocrine disorders recommend lifestyle modifications (physical activity, diet and weight loss) as 1st line therapy. Still, these strategies may be inadequate, impracticable or fail to combat metabolic alterations. Conversely, pharmacological interventions like antidiabetic drugs or antihyperlipidemic drugs have been approved to inverse metabolic dysfunctions and weight gain. Besides, their clinical use, a variety of these drugs are used off-label, such as metformin (Kouidrat et al. 2015). The reason for such use is cost effectiveness and well-tolerance to combat weight gain, so can easily be added to dietary plan and lifestyle intervention. Major disorders of endocrine system and their treatments are given in Table 1.

Melatonin is used clinically for treatment of metabolic disorders (to normalize circadian cycle), diabetes and obesity and is investigated so far in human and animal models of oxidative stress and dyslipidemia (Bonnefont-Rousselot 2014; Navarro-Alarcón et al. 2014). Thyroid related disorders like hyperthyroidism can be treated with antithyroid drugs (propylthiouracil and methimazole), radioiodine or surgery. These drugs have fewer side-effects. To achieve euthyroid condition, radioiodine in combination with β-adrenergic antagonist can be administered alongwith T3 and T4 level monitoring. Surgery is recommended if pharmacological treatment fails. Hypothyroidism treatment usually depends on age alongwith TSH level monitoring every 6-8 weeks. The prescribed dose of levothyroxine is 1.6 μg/kg/day in young patients, while in older patients the dose starts 25-50 μg/day followed by 12.5-25-μg increments every 4-6 weeks (Klein and Danzi 2007). A study showed improved cholesterol and fatigue in patients treated with levothyroxine for 12 weeks (Razvi et al. 2007). Hypercalcemia is initially treated with intravenous saline and euvolemic condition is controlled by some diuretics. Subcutaneous calcitonin and bisphosphonates can also be recommended. Parathyroidectomy can be the treatment of choice as it improves symptoms, maintains euvolemic condition and can safely be performed (Marx 2000). Medical treatment (calcimimetics, bisphosphonates, and estrogen modulators) can be considered if surgery is contraindicated. Hypocalcemia is treated with calcium and vitamin D. For acromegaly, surgical resection of pituitary mass to normalize serum IGF-1 and GH, is the 1st line therapy (Ezzat et al. 2006). If serum levels remain increased even after surgery, pharmacological treatment is advised. It includes pegvisomant (recombinant pegylated GH receptor antagonist) either as monotherapy (130 mg) or combined (77 mg) with somatostatin analog (Neggers and Vander-Lely 2009). Radiotherapy may be prescribed alongwith careful follow-up of serum IGF-1 monitoring every 6 months, if medication therapy or surgery fails (Ezzat et al. 2006).

Treatment of Cushing's syndrome involves management of hypertension (Arnaldi et al. 2003), with careful monitoring of pituitary deficiencies in case of surgical resection of pituitary adenoma. This can be treated with chemotherapeutics, including mitotane which inhibits steroid production or hormone replacement therapy. Addison's disease can also be treated with hormone replacement therapy, adequate sodium diet or hydrocortisone (20-30 mg/day), or fludrocortisone (0.05-0.1 mg/day) to mimic circadian cycle.

Medications for the treatment of diabetes include thiazolidinediones, biguanides, meglitinides, sulfonylureas, alpha-glucosidase inhibitors and insulin alongwith novel agents including incretin mimetics and DPP-4 inhibitors (Nissen and Wolski 2007; Kousar et al. 2021). Glitazones are PPAR-γ (peroxisome proliferator-activated receptor gamma) agonists are recommended for glycemic control in patients with multiple complications. Rosiglitazone and pioglitazone were approved for such treatment by FDA in 2002 (Lebovitz 2002). Among lipid lowering medications, HMG-CoA reductase inhibitors or statins, are the most commonly prescribed drugs to prevent cardiovascular and metabolic disorders as these are also well-tolerated and efficacious. For obesity therapy and weight management, orlistat (an intestinal lipase-inhibitor) and the combination of topiramate and phentermine are approved by the FDA (Pucci and Finer 2015).

Table 1: Major endocrine glands, their hormones, disorders due to hormonal fluctuations and treatment options.

Endocrine gland	Hormone	Major disorder	Treatment of choice
Pineal gland	Melatonin	Insomnia	Cognitive behavioral therapy
Hypothalamus	GHRH, TRH, CRH, GnRH, somatostatin, dopamine, vasopressin	Hypopituitarism, hypothyroidism	Hormone replacement therapy, medications, surgery
Pituitary gland	TSH, LH, ACTH, GH, MSH, PRL, vasopressin, oxytocin	Acromegaly, Cushing's disease, diabetes insipidus	Hormone replacement therapy, medications, surgery
Thyroid gland	T3, T4, calcitonin	Goiter, hypothyroidism, hyperthyroidism, autoimmune thyroid disease	Levothyroxine, methimazole, surgery, radioactive iodine treatments
Parathyroid gland	PTH	Hyperparathyroidism, parathyroid cancer, hypoparathyroidism	Vitamin D (calcitriol), calcium supplements, surgery
Liver	IGF (somatomedin), angiotensinogen, thrombopoetin, hepcidin	Metabolic disorders	Enzyme replacement therapy, medications, mineral supplementation
Pancreas	Insulin, glucagon, somatostatin	Diabetes mellitus, obesity, pancreatitis	Medications, surgery
Adrenal glands	Cortisol, aldosterone, DHEA, androgenic steroids, adrenaline noradrenaline	Addison's disease, Cushing's disease, pheochromocytomas	Hormone replacement, steroids, surgery
Ovary and placenta	Estrogen, progesterone, HCG, human placental lactogen	Endometriosis, ovarian cysts, ovarian epithelial cancer, PCOS	Clomiphene, metformin, surgery
Testis	Testosterone, inhibin	Epididymitis, hydrocele, hypogonadism	Antibiotics, anti-inflammatory drugs

Abbreviations. ACTH: Adrenocorticotrophic hormone, ADH: Anti-diuretic hormone or vasopressin, CRH: corticotropin-releasing hormone, DHEA: Dehydroepiandrosterone, FSH: Follicle-stimulating hormone, GH: Growth hormone, GnRH: gonadotropin-releasing hormone, GHRH: growth hormone-releasing hormone, HCG: Human chorionic gonadotropin, IGF: insulin-like growth factor, LH: Luteinizing hormone, PCOS: Polycystic Ovary Syndrome, PRL: Prolactin, TRH: thyrotropin-releasing hormone, TSH: Thyroid-stimulating hormone.

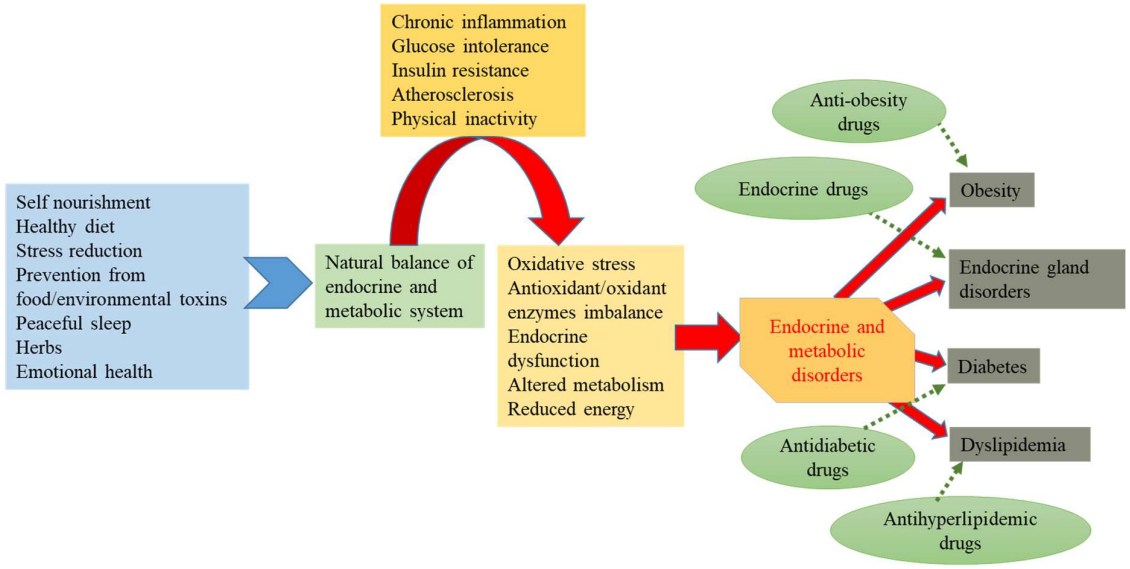

Figure 2: Factors needed to maintain the natural balance of endocrine and metabolic system and major risk factors responsible for mitochondrial dysfunction, preventing it from properly processing fuel, and no cellular energy is produced. This leads to imbalance in antioxidant/oxidant enzymes. As a result of antioxidant/oxidant enzymes imbalance and reduced energy, endocrine dysfunction and metabolic disorders occur. The potential sites of action of different drugs are presented in green ovals.

Nanocarriers in Combating Endocrine and Metabolic Disorders

Blood Triglycerides and HDL

In the recent decades, safe utilization of nanoparticles (NPs) has gained more attention of biomedical scientists and researchers for their therapeutic effects in endocrine and metabolic disorders. Studies show that silver NPs have ability to alter the levels of lactate dehydrogenase enzyme in the body; which converts dietary sugar into usable energy for cells and plays an important role in cellular respiration (Naghsh et al. 2013). But, long term use of these NPs revealed toxicity to lung tissues with abnormally raised serum biochemical and hematological parameters when experimental studies were performed on rats (Alkaladi et al. 2014).

Blood Glucose and Diabetes

Metabolic syndrome is a group of disorders characterized by high blood pressure, high blood glucose and triglyceride level. In studies, silver NPs did not much affect the blood glucose levels. Another study showed that synthetic insulin coated with dextran sulfate-chitosan nanocarrier system possesses 85% association efficacy and better controlled release was detected at pH 6.8 (Kim and Moon 2012). Ceramic nanoparticles composed of calcium phosphate, silica or titanium are more stable and biocompatible and have shown improved spatial features of insulin therapeutic effects. Rosiglitazone in form of polyethylene glycol-NPs shows improved cellular uptake of drug with anti-inflammatory response of macrophages in addition to anti-diabetic effects (Giacalone et al. 2018). Micelles having amphiphilic or surfactant molecules with hydrophobic core also exhibited controlled release of insulin in the treatment of diabetes mellitus. Besides, liposomes are small spherical vesicles with hydrophobic center and hydrophilic groups outside. Liposomes of folic acid with insulin solution showed hypoglycemic effects with 20% more bioavailability than single insulin administration in the treatment of diabetes mellitus (Li et al. 2016).

Abdominal Obesity and Tissue Fats

Obesity is associated with overweight characterized by impaired fat metabolism and can be an outcome of other pertinent diseases including cardiovascular disease, type 2 diabetes, asthma and inflammation of joints. A study has documented that gold NPs have beneficial effects for possible therapy of obesity and pertinent diseases (Chen et al. 2013). Moreover, lipid nanostructures formulation shows beneficial effects in normalizing triglycerides, cholesterol and blood glucose levels in the treatment of obesity. All these efforts combine the captivating properties of NPs with commercial application in controlling endocrine and metabolic disorders.

Bioactive Compounds in Combating Endocrine and Metabolic Disorders

Many bioactive compounds are effective in endocrine and metabolic disorders, including diabetes, hyperlipidemia and obesity. Bioactive compounds are obtained from wholegrain, fruits and vegetables exerting pharmacological effects in humans and have an essential role in the body's defense mechanisms. Such compounds are advantageous to use due to ease of accessibility, safety and fewer side effects (Gothai et al. 2016; McAnany and Martirosyan 2016). Bioactive compounds can also be obtained from microorganisms, making valuable secondary metabolites. Medicinal plants possessing different therapeutic activities like anti-inflammatory, antioxidants, antidiabetic and antihypoglycemic and anti-carcinogenic potential credited to bioactive principles (Bowling et al. 2007).

Resveratrol

Resveratrol is a stilbenoid, a kind of natural phenol and a phytoalexin that possess both anti-inflammatory and

antioxidant properties, maintains fluid homeostasis and improves mitochondrial and cellular functions. The origin of resveratrol is grapes skin, blueberries, red wines and seeds. It regulates glucose metabolism and insulin secretion from pancreatic beta cells and prevents oxidative stress (Khalid et al. 2018).

Quercetin

Quercetin is a flavonoid and documented to be effective for the treatment of DM. The main sources of quercetin are red onions, broccoli, apple and tea, and possesses antioxidant, anti-inflammatory and anti-apoptotic activities. It controls phosphorylation of extracellular signaling regulated kinase (ERK1/2) and enhances β-cell functions and glucose-induced insulin secretion (Peng et al. 2017).

Minerals

Minerals are solid substances present in nature and can be composed of one or more elements combined together. Minerals have a significant role in managing obesity. Iodine supplementation is essential for proper functions of thyroid gland and hormones. Daily intake of calcium (1200 mg) decreases fats in overweight and obese persons, whereas, low calcium intake consequences in decreased lipolysis and increased weight (Sharma et al. 2018).

Probiotics

Probiotics are live bacteria and yeasts valuable for digestive system in maintaining balance of intestinal gut flora and improving nutrient digestibility. Probiotics include *Bifidobacterium* and *Lactobacillus* and are effective for the treatment of obesity. *Bifidobacteria* and *Lactobacilli* synthesize bioactive compounds of conjugated linoleic acid, which have anti-atherosclerotic, antidiabetic, antioxidant and anti-obesity properties (Rashid et al. 2020).

Phytochemicals

Phytochemicals are the compounds produced by plants such as carotenoids, triterpenes and polyphenols (flavones, flavonoid, flavonols, phenolic acids, curcuminoids, stilbenes and anthocyanins) and possess antioxidative, antiadiposity and cardioprotective activities. Certain phytochemicals act as thermogenic compounds including caffeine, salicylic acid, ephedrine and capsaicin, and prevent excessive accumulation of fats in body tissues by burning extra calories (Zheng et al. 2009).

Cinnamon

Cinnamon is a spice made from the inner bark of trees of genera *Cinnamomum*. It is filled with antioxidant properties and a number of other beneficial effects in the treatment of endocrine and metabolic disorders related to insulin sensitivity, glucose and lipid metabolism, oxidative stress, inflammation and body weight (Hussain et al. 2019, 2021).

Curcumin

Curcumin is a polyphenolic compound produced by plant rhizome of *Curcuma longa* specie, possessing anti-inflammatory, antioxidant and antitumorigenic properties. Curcumin decreases oxidative stress by inhibiting aconitase enzyme of citric acid cycle (Sjögren et al. 1996). It also decreases lipogenesis by enabling β-oxidation of fatty acids and is beneficial in endocrine disorders (Noorafshan and Ashkani-Esfahani 2013).

Preventive Strategies of Endocrine and Metabolic Disorders

Restriction of Food Toxins

Physiologically, hormones are present in continuous fluctuations and any imbalance in their levels is primarily due to dietary habits of a person. Different chemicals, preservatives, colorants and refined sugars are routinely used by food industry, additionally, junk food contains higher quantities of salts and trans-fatty acids which can alter hormonal balance in body. Smoking and alcohol abuse should also be avoided. The need is to restrict unhealthy food containing excessive fats, chemicals or extra sodium to maintain body hormonal levels normal (Maqbool et al. 2016).

Sleep Quality

A good quality sleep refers to take 6-8 hour night sleep, which is beneficial in keeping the glands healthy for normal production, metabolism and maintenance of hormones. A medical condition called insomnia or sleeplessness arises as a result of irritability or stress that may cause poor functioning of glands, lessen immunity, weight gain and restricted cognitive ability (Ruge et al. 2019). Melatonin hormone regulates the sleep-wake cycle and has therapeutic effects for sleep disorders. Some food materials containing antioxidants (e.g., chamomile tea) aid in maintaining better quality of sleep and decrease the occurrence of insomnia while some other disturbs sleep patterns include alcohol, smoking and caffeine beverages, so should be avoided at bedtime (Adib-Hajbaghery and Mousavi 2017).

Stress Management

Little stress is essential for survival and protection of human and animal health, however, chronic stress possess devastating effects on body organs and glands that may harm physical and mental status (Hartney 2020). Stress and anxiety are common problems of society and can ruin the balanced life. In females, chronic stress can postpone or stop ovulation while in males, it can result in low testosterone levels. The goal of therapy is to avoid or reduce the negative outcomes of stress on body. Stress management therapy includes calming and relaxing the mind, positively controlling the emotions and handling stress peacefully. Besides, physical activity provides a better solution in stress management as it reduces stress hormonal levels and enhances neuronal production of endorphins to feel good. Routine exercise helps in lowering body's cortisol levels and maintaining endocrine and metabolic balance (Bittar et al. 2016; Krause et al. 2019). Yoga and meditation practice are beneficial approach for controlling stress and emotions, improving cognition, balancing hormones, relaxation, self-discovery and awareness, and keeping spiritual harmony with nature. Stress reducing major food items includes chocolates, coffee, walnuts, banana, oranges, fish, oats, eggs, tea, wholegrain and probiotics (Singh 2016).

Reduce Exposure to Environmental Toxins

A number of environmental toxins are responsible for hormonal imbalance when the body fails to eliminate the toxic chemicals. This leads to toxicity of inner body environment resulting in metabolic and endocrine disorders. So the solution is to avoid bodily exposure to chemicals by adapting preventive measures, including unnecessary usage of drugs, pesticides, household chemicals, deodorants, sunlight exposure and radiations. A healthy food with antioxidants, dietary fibers and probiotics are necessary to regulate and maintain a normal body hormonal level and metabolism (Zheng et al. 2018).

Conclusion and Recommendations

The chapter summarizes the endocrine system physiology comprising of endocrine glands, their respective hormones, disorders of endocrine and metabolic system as well as their therapeutic strategies. The synchronized and balanced hormonal production by endocrine glands is essential for maintenance of good health. Any fluctuation either in production or release of hormones disturbs the body homeostasis and give rise to various metabolic disorders, some of which are life threatening. Pharmacological interventions aim to identify and treat specific metabolic and endocrine disorders. Besides, nanocarriers and bioactive compounds show promising effects to interact with living systems with better health outcomes. Latest research on beneficial use of bioactive compounds in endocrine and metabolic disorders is presenting significant growth and will be upcoming in future. Balanced and nutritious food, stress management and sleep quality together with active life style are essential to retain normal endocrine and metabolic functions and play crucial role for emotional and hormonal health.

Confliction of Interest Statement

All the authors declare no confliction of interest in anyway.

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