Metabolic Syndrome Components in Patients with Pituitary Adenoma

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ABSTRACT

Pituitary adenomas are benign tumors of the anterior portion of the pituitary gland (adenohypophysis), representing the 25 % of all the tumor alterations. Pituitary adenomas are classified by the type of hormone secreted, cellularity, size, and structural alterations by the hormonal segregation. The diagnosis consists on the histopathological identification of cell types and the image-guided by magnetic resonance or tomography; the treatment can be both pharmacological and surgical. Metabolic Syndrome is the set of clinical conditions that increase the risk of cardiovascular diseases with an estimated prevalence of 25 % worldwide. The alterations of metabolic syndrome are obesity, hypertension, dyslipidemia, insulin resistance, and diabetes mellitus type II. Pituitary adenomas and metabolic syndrome have an important relationship, hormone-secreting by pituitary adenomas affects a myriad of signaling pathways, which allows a favorable environment for the appearance of the metabolic syndrome. Moreover, patients with pituitary adenomas are shown to have an improvement in metabolic parameters after the medical/surgical treatment. The objective of this review is to explore the possible mechanisms through which PAs contributes to MetSx.

Introduction

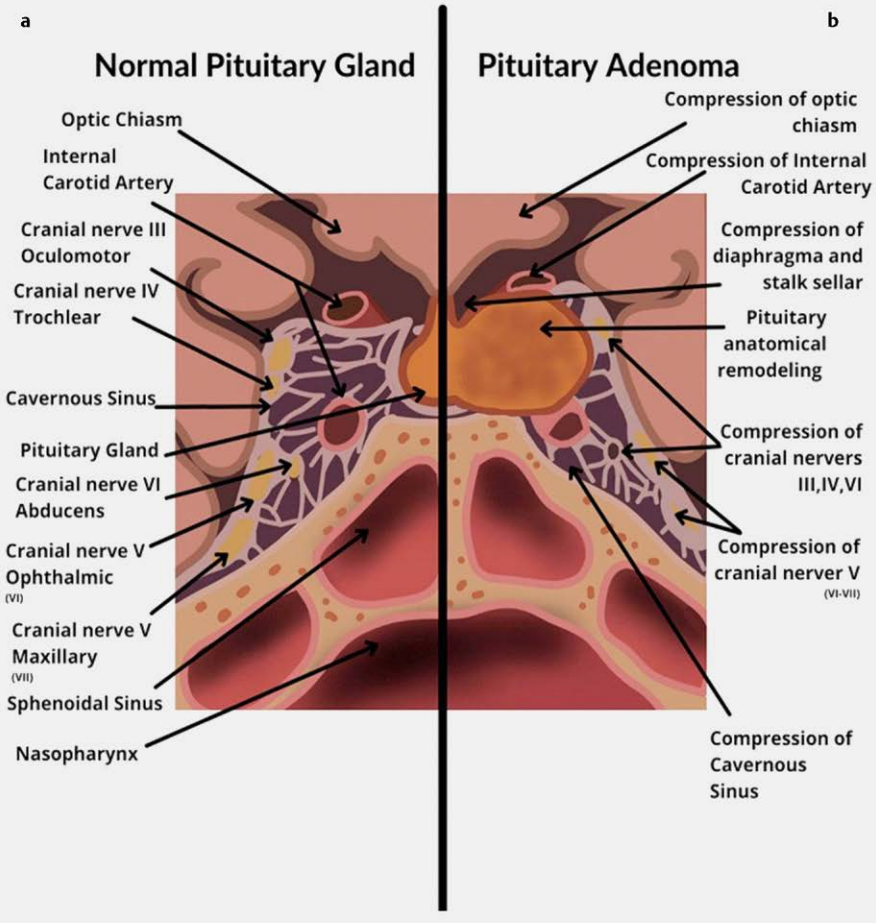
Pituitary adenomas (PAs) are defined as benign tumor of the anterior pituitary, nevertheless, it is considered a true neoplasm [1, 2]. These tumors constitute about 10 % of all intracranial neoplasms, and 25 % of all intracranial neoplasms surgically removed [3]. PAs are closely related to Metabolic Syndrome (MetS), an entity that refers to the co-occurrence of several known CV risk factors, including insulin resistance (IR), obesity, atherogenic dyslipidemia, and hypertension (HT) [4]. A higher prevalence of MetS (54 %) and its components has been observed in patients with pituitary adenoma compared to the general population [5]. This phenomenon was previously observed by Zheng and colleagues who proposed the monitoring of metabolic parameters before and after surgery based on the association between PAS with these entities [6]. The coexistence of PAs and MetS is common, however, this relationship and the possible pathways involved have not been fully established; for this reason, the objective of this review is to analyze the pathophysiological relationship and clinical predisposition between PAs, hormonal subtypes, and the development of MetS.

Pituitary adenoma

It is thought that PAs are formed by a process that involves clonal expansion of single abnormal cells owing to somatic genetic mutations or chromosomal abnormalities [7]. Among the main risk factors associated with PA is the presence of obesity, however, the relationship between PA and obesity is scarcely explored [8]. The PAs are typically classified according to their cellular origin and their size [9]. Related to their size, or Wilson–Hardy classification, the PA can be microadenomas if they are smaller than 1 cm, or macroadenomas if their size is 1 cm or more altering the anatomy of the selar region as shown in ▶ **Fig. 1**. Regarding the cellular origin, the PA can rise from any kind of cell located in the anterior hypophysis, producing or not hormones of the given cellular linage; in the first case, these adenomas are called functional, and in the latter case, they are called non-functional. Functional PAs can be classified as gonadotroph, thyrotrope, corticotrope, lactotroph, somatotroph, or plurihormonal [10].

Currently, the prevalence of clinically relevant pituitary adenomas is about 1 per 1000 of the general population, whereas the general incidence of PA is 3.9 to 7.4 cases per 100 000. Prolactinomas and nonfunctioning PA are the most frequent subtypes, followed by somatotroph and corticotrope adenomas [7]. Patients with PA generally present with neurological symptoms caused by the compression of the surrounding structures, "mass effect", or as incidental findings in radiological studies made for other reasons. Characteristically, the PA can also present through hormonal disturbances. In patients with non-functional PA, the most common symptom is bitemporal hemianopia [10]. Furthermore, PA is manifested accordingly to its cellular lineage: somatotroph presents with acromegaly; lactotroph with hyperprolactinemia; corticotrope with hypercortisolism or Cushing syndrome; thyrotrope with hyperthyroidism; and gonadotroph is presented with sexual disturbances [3].

Magnetic resonance (MR) is the gold standard for the diagnosis of PA, however, there are no pathognomonic signs described. On the other hand, it is mandatory to explore laboratory findings to determine the function of the hypothalamus-pituitary axis. The treatment could differ according to the type of PA, which is addressed in ▶ **Table 1**.



▶ **Fig. 1** Anatomy of the selar region and modification of the structure secondary to pituitary adenoma: **a**: Normal anatomy of the selar region, where several cranial nerves and the carotid artery are observed as well as the cavernous sinus with its venous confluence and the sphenoidal sinus at its base. **b**: Pathologic modification of the selar region, with compression of the cranial nerves, optic chiasm, carotid artery, and affectation of the pituitary anatomy, which give the symptomatology of visual alterations, headache, hydrocephalus, rhinorrhea, etc.

▶ **Table 1** Treatments for each type of adenoma.

Adenoma type	First line [Ref]	Second line [Ref]	Third line [Ref]
Lactotroph	Pharmacologic (DA) [11]	TSS [12–13]	RT [14]
Somatotroph	TSS [15]	Pharmacologic [16]	RT [14]
Corticotroph	TSS [17]	Pharmacologic (adrenal enzyme inhibitors, adrenolytic agents, or glucocorticoid-receptor antagonists) [19]	RT [14]
	RT (for children under age 18 years)* [18]		Bilateral total adrenalectomy (may be preferred by the patient)* [20]
Thyrotroph	TSS	Pharmacologic (somatostatin analogues) [22]	RT [23]
	Pharmacologic before surgery to restore euthyroidism (somatostatin analogues)* [21]		
Gonadotroph	TSS [24]	RT [25]	–
Non-functioning	TSS [24]	RT [25]	–

TSS: Transsphenoidal surgery; RT: Radiotherapy; DA: Dopaminergic Agonist. *: Therapeutic alternative

▶ **Table 2** Definition of metabolic syndrome by different organizations.

	WHO 1999	EGIR 1999	AACE 2003	NCEP ATP-III 2005	AHA 2005	IDF 2009
Criteria	IR + any other 2	IR + any other 2	≥ 2 items	≥ 3 items	Any 3 or 5	≥ 3 items
Insulin resistance	IR in the top 25 %	Plasma insulin > 75 PH percentile	High risk of IR	–	–	–
Blood glucose	Fasting glucose > 110 mg/dl or 2-hour glucose > 140 mg/dl	Fasting glucose 110 to 125 mg/dl	Fasting glucose ≥ 110 mg/dl or ≥ 2-hour glucose ≥ 140 mg/dl	Fasting glucose ≥ 100 mg/dl or drug treatment	Fasting glucose ≥ 100 mg/dl (includes diabetes)	Fasting glucose ≥ 100 mg/dl or drug treatment
Blood pressure	≥ 140/90 mmHg	≥ 140/90 mmHg or drug treatment for HT	≥ 140/90 mmHg	≥ 130/85 mmHg or drug treatment	≥ 130/85 mmHg or drug treatment	≥ 130/85 mmHg or drug treatment
Dyslipidemia	TG ≥ 1.7 mmol/l HDL-C < 0.9 mmol/l (35 mg/dl) (men); < 1.0 mmol/l (40 mg/dl) (women)	TG ≥ 1.69 mmol/l (149 mg/dl); HDL- C < 1.0 mmol/l (40 mg/dl) for men and women	HDL-C < 1.0 mmol/l (40 mg/dl) (men); < 1.3 mmol/l (50 mg/dl) (women)	TG ≥ 150 mg/dl, HDL-C < 40 mg/dl (men); < 50 mg/dl) (women) or drug treatment	TG ≥ 150 mg/dl or HDL-C 40 mg/dl (men) < 50 mg/dl (women) or drug treatment	TG ≥ 150 mg/dl or HDL-C 40 mg/dl (men) < 50 mg/dl (women) or drug treatment
Obesity	Waist/hip ratio > 0.9 (men); > 0.85 (women) and/or BMI > 30 kg/m^2	Waist ≥ 94 cm (men) or ≥ 80 cm (women)	BMI ≥ 25 kg/m^2 or waist ≥ 102 cm (men) or ≥ 88 cm (women)	Waist ≥ 102 cm (men) or ≥ 88 cm (women)	Waist ≥ 102 cm (men) or ≥ 88 cm (women)	Waist ≥ 94 cm (men) or ≥ 80 cm (women)

Metabolic syndrome

MetS (syndrome x, insulin-resistant syndrome, etc.) establishes the set of CV risk factors that may lead to Diabetes Mellitus Type 2 (DM-II) [26, 27]. This term was coined in 1970 by Herman Haller; however, until 1999 the World Health Organization (WHO) set an international definition, from which multiple organizations have built their definition around the same core including central obesity, hypertension (HT), hypertriglyceridemia, decrease in HDL-C and dysglycemia, nevertheless, each organization defines its risk standards and thresholds [28] (▶ **Table 2**). Currently, MetS constitutes a serious global health problem since it affects around 20–25 % of people in the world [29]. This high prevalence makes the study of MetS vital importance because it coexists with various other alterations, as in this case of PAs.

Metabolic syndrome and pituitary adenoma

Pathways

There is growing evidence associated with the development of neoplasms and the mortality related to MetS or its components [30–32]. It has been suggested that there are multiple pathways deregulated in neoplasms that can be synergic, such as IR, the insulin-like growth factor (IGF)-1 system, adipokines, fatty acids, and its aromatase activity [30], as well as oxidative stress and the subsequent impairment to the DNA repair [31], which promotes cell migration, and resistance to apoptosis [32].

Improvement after treatment

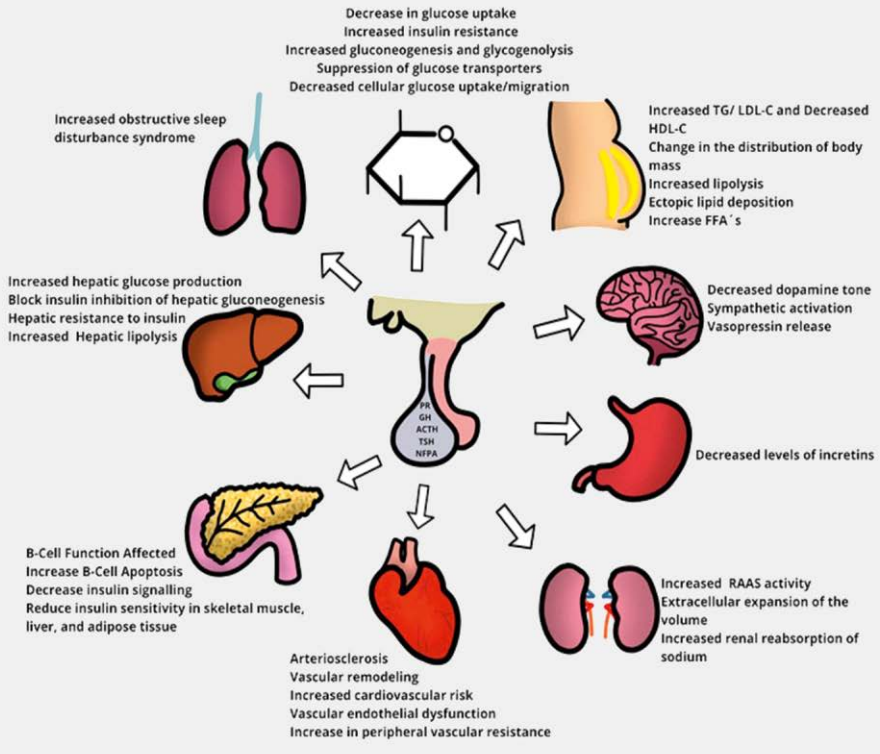
Furthermore, in certain types of PAs, a relationship with weight gaining, MetS, and IR [33–36] has been observed. Nevertheless, these parameters have been not normalized after the surgical treatment and the results obtained are usually contradictory [37–41]. Likewise, most of the studies are developed in patients with non-functioning, somatotroph or lactotroph adenomas, so the information is scarce with respect to the rest of the adenomas, and mostly the treatment evaluated is pharmacologic [42].

The improvement of the metabolic parameters after the treatment is an expected outcome, if it is explained through the underlying mechanisms of the disturbances given by the pituitary disease, the main theories turn around two mechanisms: due to mechanical compression of the hypothalamus leading to dysregulations in the metabolic pathways, or due to endocrinological disturbances or famine of certain hormones [35–40]. PAs can be thought in bidirectional pathway that feedback by itself, promoting the tumor development in the presence of MetS or its components, and once the tumor is established leads to metabolic alterations as is shown in ▶ **Fig. 2**.

Pathphysiological association between pituitary adenoma (hormonal segregation) and obesity

Prolactine

Prolactine (PRL) is a hormone secreted mainly by the front part of the pituitary gland. Its multiple functions are related to the immune, endocrinological, nervous, and metabolic systems. PRL also regulates homeostasis, growth, and development mechanisms [43]. In pathological states due to prolactin-secreting pituitary adenomas, typical alterations such as galactorrhea, amenorrhea, headache, and visual disturbances have been identified; however, hyperprolactinemia has been related to weight gain/obesity, hyperphagia, increased adipose tissue, glucose intolerance, IR, increased ME/LDL-C, decreased HDL-C, and MetS [44]. The mechanism by which hyperprolactinemia is related to these alterations is not clear, however, various pathophysiological mechanisms have been proposed to explain it, among the most important are the decrement of dopamine tone (DT), leptin resistance, low levels of adiponectin, increased B-cell function, the reduction of the Lipoprotein Lipase (LL) activity [45, 46] and the dysregulation of carbohydrate and lipid methabolism. Several studies have analyzed the role of PRL as a promoter for obesity, it has been identified that pa-



▶ **Fig. 2** Main pathophysiological alterations according to each organ, secondary to hormones secreted by the adenohypophysis**:** Main pathophysiological modifications secondary to hormonal influence in each system, metabolic alterations together with cardiovascular alterations are most frequently found independently of the stimulating hormone.

tients with hyperprolactinemia (mostly those with macroadenoma) tend to develop obesity. Moreover, the administration of dopaminergic agonists (DA) decreases PRL levels and reduces the fasting plasma glucose, which lead to decreased serum LDL-C and TG levels, as well as increased insulin sensitivity [47, 48].

Growth hormone

Growth hormone (GH) is secreted by the front portion of the pituitary gland. Its functions includes the induction of longitudinal growth and various anabolic and catabolic metabolic processes, which are the result of both GH and insulin-like growth factor type 1 (IGF-I) secretion. GH hypersecretion secondary to a pituitary tumor conditions the development of acromegaly, a pathology where various metabolic alterations are evidenced. Although GH and IGF-I are elevated, the phenotypic alterations depend on GH hypersecretion [49]. One of the main phenotypic alterations of GH hypersecretion is the change in the distribution of body mass, characterized by a decrease in fat mass and an increase in lean mass. Among the identified pathophysiological alterations, the following can be mentioned: decrease in adiponectin release, decrease in the LL activity, decrease in leptin secretion, catabolic activity promoting lipolysis, the release of free fatty acids (FFA), decrease in glucose uptake, increased hepatic glucose production, decreased adipogenesis and adipokine secretion mechanisms that disrupts the insulin sensitivity and provide ectopic lipid deposition [50, 51].

Adrenocorticotropic hormone

The secretion of cortisol begins in the hypothalamus, where the adrenocorticotropin-releasing hormone is produced, the latter is secreted in the anterior part of the pituitary gland where it subsequently stimulates the production of adrenocorticotropic hormone (ACTH), which in turn stimulates the cortex of the adrenal gland for the formation of cortisol. Cortisol participates in various metabolic and immunological functions, electrolyte transport, and catabolism, among other functions [52]. Hypercortisolism is related to the time to cortisol exposure, leading to differentiation and proliferation of adipocytes mainly in the central visceral tissue promoted by an overexpression of adipogenic factors and expression of 11β-hydroxysteroid dehydrogenase [53]. Hypercortisolism affects the carbohydrate metabolism and insulin sensitivity, and there are also dysregulations in lipid metabolism (there is an increase in LL activity and lipolysis). Moreover, leads to alterations in food intake promoting a state of "stress" increasing the appetite, likewise, there is an increase in the secretion and leptin resistance [53]. States of hypercortisolism related to pituitary adenomas (most frequently microadenoma) have been related to metabolic alterations, increased CV risk, and redistribution of adipose tissue (from the periphery to the center) [54].

Thyroid-stimulating hormone

Thyroid-stimulating hormone (TSH) is secreted by thyrotrophic cells in the anteromedial portion of the pituitary gland, in turn, it contributes to the stimulation of thyroid hormones (THs) which fulfill various functions in the metabolism of carbohydrates and lipids [55, 56]. The prevalence of a TSH-secreting pituitary adenoma is 0.5 to 2 % with an estimated 1/2 cases per million inhabitants. A state of hyperthyroidism has been directly associated with metabolic alterations and distribution of body mass [57]. Among the most important pathophysiological alterations are: states of adrenergic hyper-stimulation, increased thermogenesis, basal metabolism (increased catabolic pathways), oxygen consumption, intestinal transit, anorexia, secretion of leptin and ghrelin. All these alterations are translated into a higher metabolic expenditure, therefore a reduction in lean and fat mass [56, 58].

Non-functioning pituitary adenoma

Non-functioning pituitary adenomas (NFPAs) are benign tumors originating from cells of the adenohypophysis without clinical evidence of hormonal secretion, generally, they usually present with compressive alterations such as headache, visual disturbances, pituitary apoplexy, and hyperprolactinemia (generally not higher than 2000 mU/l/100 ng/ml) [59]. Hyperprolactinemia is produced by mass effect and secondarily a decrease in DR. Among the main alterations related to hyperprolactinemia, we have mentioned resistance to leptin, reduction of adiponectin, hyperphagia, and IR [60, 61].

Pathophysiological association pituitary adenoma (hormonal segregation) and hypertension

Polactine

The increment in PRL levels has been mainly related to metabolic and CV alterations. Within the vascular alterations are arteriosclerosis, vasoconstriction due to high levels of PRL, increased pressor response to angiotensin II, decreased production of nitric oxide (NO), endothelial dysfunction, inflammation and dysfunction, and vasodilator inhibition [62–64].

Growth hormone

Among the complications of acromegaly are metabolic, respiratory, and CV alterations which represent 80 % of complications with the highest negative prognosis. The prevalence of arterial HT in acromegaly varies from 11 % to 50 % of all patients, with a cut-off point in 33 % or 1/3 of all patients; the rate of negative prognostic is related to the exposure time to GH/IGF-1 [65, 66]. Within the typical CV alterations, HT has been described as a pathophysiological mainstay for the development of complications. Various routes of CV damage have been identified to develop HT induced by overexposure to GH/IGF-1, which are:

- Extracellular expansion of the volume secondary to the anti-natriuretic effect of GH. An increment of aldosterone because of GH in turn increases the activity of the renin-angiotensin-aldosterone system (RAAS) allowing the reduction in the secretion of atrial natriuretic peptide [65–67].
- Increment in peripheral vascular resistance due to increased RAAS activity: growth of smooth muscle cells due to the effect of GH (vascular hypertrophy), sympathetic activation, and endothelial dysfunction [65–67].

Adrenocorticotropic hormone

HT is a frequent complication in states of hypercortisolism with a prevalence that reaches up to 85 %. Several pathophysiological fac-

tors have been identified, which cause HT, however, the activation of RAAS, mineralocorticoid activity, sympathetic activation, excess of glucocorticoids (GCs), the vaso-regulatory system, and water retention seem to play a fundamental role in the genesis of HT in these patients [68]. RAAS is the most investigated system as a primary factor for developing HT in hypercortisolism states, an increase in angiotensinogen, renin depression, increased receptors for angiotensin II (type 1 A) and activation of angiotensin have been found as a neurotransmitter increasing sympathetic activity and vasopressin release [68–70]. Another important mechanism is the high amount of GCs, the enzyme hydroxysteroid dehydrogenase type 2 (11β-HSD2) converts cortisone into cortisol, disabling its binding to the mineralocorticoid receptor, however, in hypercortisolism states the renal 11β-HSD2 is saturated by an excess of cortisol, therefore cortisol binds to the mineralocorticoid receptor, causing renal sodium retention, potassium excretion, and increased blood volume causing HT [71].

The high concentration of GCs also increases the sensitivity to peripheral vasopressors such as norepinephrine. In addition, a greater secretion of the vasoconstrictor endothelin 1(T-1) has been documented, which also favors early atherosclerosis and a decrement in the secretion of nitric oxide synthase (NOS) molecule required for vasodilation [68–71]. Last but not least, hypercortisolism is a vascular remodeling secondary to HT due to the excess of GCs, which promotes angiogenic factors such as vascular endothelial growth factor (VEGF) and insulin, the characteristics of these changes are an increased resistance in the media and lumen, an increment of the middle layer and the thickness of the vascular wall [68, 71]. An increment in body fat can lead to obstructive sleep disturbance syndrome (OSAS), which can exacerbate HT by increasing sympathetic tone, IR, and diabetic autonomic neuropathy [70, 71].

Thyroid-stimulating hormone

TH has direct and indirect regulation on hemodynamic metabolic and CV functions. In hyperthyroid states, the main alterations are increased resting heart rate, increased total blood volume, increased stroke volume, RASS activation, increased contractility myocardial, increased ejection fraction, decreased peripheral vascular resistance with consequent increased cardiac output and HT [72–74]. One of the best-known pathophysiological mechanisms is an increase in heart rate (increased preload), and a reduction in peripheral resistance secondary to the action of T3 on vascular smooth muscle. This reduction in resistance also affects the renal system, which, upon a decrease in perfusion, activates RASS and increases hepatic/cardiac renin levels, increasing sodium reabsorption and increasing total blood volume, increasing cardiac output, and hypertensive states [73, 74]. THs also affect some other important hemodynamic factors such as an atrial natriuretic peptide, brain natriuretic peptide, T-1, and the vasodilator polypeptide adrenomedullin are increased and can induce HT due to their effects on the tone of blood vessels, arterial stiffness states, sodium retention, increased blood level and myocardial remodeling [72, 75]. A poorly-studied mechanism is the stimulation of T3 on the production of erythropoietin and the synthesis of erythrocytes, further increasing the total circulating volume [75]. CV complications are highly prevalent in hyperthyroid patients (atrial fibrillation, hypercoagulability, pulmonary embolism, cardiac inefficiency, coronary artery disease) the morbidity and mortality related to these complications are high as well as the persistence of HT and complications secondary to their comorbidities [72, 74, 75].

Non-functioning pituitary adenoma

The pathophysiological mechanisms of HT are clearly described in patients with most hormonal variants of PA, However, in NFPAs more studies are needed to determine its relationship with the development of HT.

Pathophysiological association between pituitary adenoma (hormonal segregation) and dysglycemia

Prolactine

There are several publications that associate PRL with an increased response of the B-Cell favoring insulin secretion, however, several studies conclude that the PRL has adverse effects on carbohydrate metabolism which predispose to stages of IR and DM-II thus, the role of PRL in dysglycemia is not fully established [76]. PRL induces the dopaminergic inhibition, which leads to hyperphagia and secondarily to obesity with altered carbohydrate metabolism and IR, it has been shown that PRL decreases insulin secretion. PRL promotes IR and DM-II though adiponectin and IL-6 inhibition; Moreover, PRL directly affects LL and reduces lipogenesis. There is evidence that the therapy used with DA such as bromocriptine improves insulin sensitivity [77–79].

Growth hormone

Among the complications of GH hypersecretion (acromegaly) are alterations in the metabolism of lipids and carbohydrates, IR is the main alteration for hyperglycemia (DM-II, IGT, and ATF) in patients with acromegaly, it has an approximate prevalence of 16–56 % [80]. The diabetogenic effects of GH are explained by the antagonizing action with insulin, GH promotes gluconeogenesis and glycogenolysis creating a hyperglycemic environment, likewise, it increases lipolysis with the second increase in FFA which increases the competition between glucose and FFA with the consequent decrease in the use of glucose in the muscle, at the same time, the increase in FFA induces IR which is the main pathophysiogenic mechanism induced by GH explaining the alterations in carbohydrate metabolism of patients with acromegaly [80–82]. GH induces IR, which is usually compensated by hyperfunctionality of pancreatic B-cell with its consequent functional impairment and reduced insulin secretion. Another key pathophysiological mechanism is the inhibition of insulin signaling pathways necessary for the transport and peripheral use of glucose, as well as suppression of glucose transporters (GLUTS 1 and 4) induced by GH [80–82].

Adrenocorticotropic hormone

One of the most common complications in ACTH hypersecretion is the alteration in glucose metabolism reaching 43–84 %, increasing the risk of concomitant comorbidities and increased risk of CV mortality [83]. GCs affect the metabolism of carbohydrates directly and indirectly, is proportional to the time and concentrations of

exposure, the main alterations by which a diabetogenic environment is generated, is the ability of GCs to reduce insulin sensitivity in skeletal muscle, liver, and adipose tissue as well as impair B-cell function [83, 84]. GCs can block insulin inhibition of hepatic gluconeogenesis as well as promote its stimulation by increasing hepatic glucose secretion, promotes the decrement of cellular glucose uptake/migration, hepatic and peripheral by inducing cell receptor defects, and perform an inhibition of muscle glycogen synthesis dependent on GC's [85]. Proteolysis and lipolysis increase the amount of FFA and free amino acids, decrease insulin signaling, increase IR in peripheral tissues and decrease their sensitivity. Proteolysis predisposes to a decrement in muscle mass with impaired glucose uptake capacity in this tissue, there is also a higher visceral adipose tissue which increases the risk of developing MetS, producing inflammation, secretion of adiponectin and leptin, and promoting IR [84, 86, 87]. GCs bind to B-cell receptors affecting the transport and metabolism of glucose, in addition, they reduce their ability to adapt to hyperglycemic environments, generating hyper functionality due to the IR leading to cell apoptosis [87].

Thyroid-stimulating hormone

Carbohydrate metabolism disorders are common alterations in hyperthyroidism, up to 50 % of hyperthyroid patients develop glucose metabolism disorders; THs produce IR, poor control uptake of glucose in circulation, and decreased insulin secretion [88, 89]. Hepatic gluconeogenesis and glycogenolysis are increased by THs, there is a higher concentration of glucose with a secondary increment in circulating insulin, however, there is hepatic resistance to insulin developed by THs so it develops glucose intolerance and decreased use in peripheral tissues, there is greater antagonism with insulin and indirectly greater activity by glucagon and catecholamines [88]. TTHs increase lipolysis in adipose tissue and muscle proteolysis with the release of glycerol, amino acids, and FFA which are used as substrates for gluconeogenesis and secondarily increase glucose, in addition, this elevation of substrates also intensifies the IR. Another mechanism favoring the alteration of carbohydrate metabolism is the increment of B-cell apoptosis [89].

Pathophysiological association between pituitary adenoma (hormonal segregation) and dyslipidemia

Hyperprolactinemia

Alterations in the lipid profile are common in patients with hyperprolactinemia characterized by an increase in LDL-C, TG, and a decrease in HDL-C. It has been shown in various studies that treatment with DA and pituitary surgical treatment help noticeably reduce the levels of LDL-C, TG and as well as increase the levels of HDL-C in 6–12 months [90–92].

Growth hormone

The prevalence of lipid metabolism disorders in patients with GH hypersecretion ranges between 30–50 %, being one of the most common alterations. Among the typical alterations are hypertriglyceridemia (increased TG and LDL-C). and decreased HDL-C, there is a close relationship of alterations in the metabolism of lipids and carbohydrates that culminate in IR and reduction in body fat [93, 94]. GH promotes lipolysis in adipose tissue with an increase in circulating FFA, which leads to the formation of VLDL-C that promotes IR, in turn, GH reduces the activity of LL in adipose tissue, blocking TG uptake in adipose tissue by increasing hepatic FFA circulation [93, 94]. The elevation of pro-atherogenic lipoproteins (Lp-a, Apo AI, and Apo E) cause damage in the arterial endothelium promoting vascular dysfunction, with the infiltration of mononuclear cells in the sub-endothelial space and increased the CV risk. In addition, IGF -1 promotes the decrement of lectin-cholesterol-acyl-transferase, an enzyme that converts free cholesterol to HDL-C [93].

Adrenocorticotropic hormone

The alteration of lipid metabolism is frequent alteration hypersecretion of GCs with a percentage between 30–70 %, cortisol regulates catabolic metabolic pathways (lipolytic and adipogenic processes); the alteration of the lipid profile is characterized by the increase in total cholesterol, LDL-C and TG with decreased HDL-C levels [95, 96]. The GCs promote the release of FFA from mature adipocytes through the expression of hormone-sensitive lipase (HSL), this increment in lipogenesis promotes the storage of hepatic lipids and in the skeletal muscle, the GCs increase the lipolysis by modifying cyclic adenosine monophosphate (cAMP) levels activating the protein kinase A (PKA) which modulate the response to hormones such as catecholamines and GH [96]. The effect of the GCs differs according to its temporality, in the short term its main effect focuses on catabolic actions in lipid metabolism, while the chronic effect induces a pro-adipogenic effect. In addition, GCs promotes the LL activity increasing the uptake of TH in adipose tissue [95, 96].

Thyroid-stimulating hormone

Hyperthyroidism is a pathology with low prevalence (2–3 %), hyperthyroid patients present few lipid metabolism alterations, the main is the decrease in LDL-C and HDL-C, meanwhile TH may be increased, decreased, or remain normal [97, 98]. TH stimulates the degradation and synthesis of lipids, however, the catabolic pathways are mainly hepatic lipolysis and in adipose tissue, lipolysis generates more circulating FFA, which can travel to the liver esterifying to triacylglycerol which leads to a stimulation of hepatic lipolysis through glucose metabolism [98, 99]. LDL-C decrement is caused mainly by an increase in its receptors stimulated by THs, which leads to greater catabolism of the LDL-C particles; HDL-C is also decreased by an increase in its catabolism and donations of cholesterol esters to other lipoproteins. However, although cholesterol is increased, there are anti-regulatory mechanisms for its homeostasis, such as the uptake and elimination of cholesterol, converting it into bile acids, and eliminating it; THs also decrease dietary uptake of cholesterol [97, 100].

Non-functioning pituitary adenoma

As mentioned above, metabolic alterations correlated with NFPAs are not clearly described, alterations related to lipid metabolism are not the exception, alterations in the lipid profile that improve after surgery have been described, as mentioned possibly anterior to the PRL-induced effect.

Conclusions

This review highlights the pathophysiological relationship and clinical predisposition between PAs, hormonal subtypes, and the development of MetS. Metabolic alterations differ according to the hormonal type, however, among the most frequent are IR, dyslipidemia, HP, and obesity. There are several pathophysiological pathways and several organs involved in the development of biochemical alterations, and nowadays the evidence evaluates the therapy (pharmacological and surgical) with the improvement of the parameters that characterize the MetSat 6 and 12 months after its application, thus defining a central point in the clinical and pathophysiological relationship between PAs and MetS. In this manuscript, we used a general definition of MetS, however, the heterogeneity of this syndrome and the genetic background of high-risk populations must be taken into consideration for clinical trials. As we can see, the relationship between these entities is well defined; however, the information found in clinical is still limited, further investigations are needed focusing on the clinical, diagnostic, pathophysiological and therapeutic studies.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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