Review

An Overview of Cardiovascular Risk in Pituitary Disorders

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An Overview of Cardiovascular Risk in Pituitary Disorders

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Abstract: Cardiovascular morbidities are the main cause of mortality in pituitary disorders accruing either from hormonal excess or deficiency. Cushing disease is associated with various cardiovascular abnormalities;visceral obesity, insulin resistance, atherosclerosis, arterial hypertension, dyslipidaemia and hypercoagulability, structural and functional changes in heart, which do not seem to reverse completely even after remission. Acromegaly is related with insulin resistance, but also with structural and functional heart changes which consist acromegalic cardiomyopathy. Patients with prolactinomas demonstrate an aggravation of metabolic parameters, obesity, dysregulation of glucose and lipid metabolism and endothelial dysfunction. On the other hand, hypopituitarism and conventional hormonal replacement which is far from ideal contribute to an unhealthy metabolic status which leads to atherosclerosis and premature mortality. This review aims to update literature on cardiovascular risk and relevant morbidities in pituitary disorders.

Keywords: cardiovascular disease; pituitary; acromegaly; Cushing's disease; prolactinoma; hypopituitarism

Introduction

Pituitary gland plays a pivotal role in the regulation of metabolism and the cardiovascular status. Glucocorticoids increase caloric and dietary fat intake, induce hyperglycemia and ectopic fat distribution and act directly on the heart and blood vessels. Cushing's disease (CD) is associated with visceral obesity, insulin resistance, atherosclerosis, arterial hypertension, dyslipidaemia and hypercoagulability, structural and functional changes in the heart. GH promotes insulin resistance and lipolysis and regulates cardiac contractility and vascular motility. Acromegaly may result in glucose and lipid abnormalities and various structural and functional heart disorders characterized as acromegalic cardiomyopathy. Prolactin regulates food intake and exerts inotropic action on myocardium. Patients with prolactinoma have frequently endothelial dysfunction and even abnormalities of systolic and diastolic heart function. Hormonal excess or deficiencies commonly caused by pituitary adenomas are associated with several morbidities; the cardiovascular burden is the most important and the main cause of mortality. Various treatment modalities (surgery, medical treatment or radiotherapy) of pituitary adenomas may also affect the cardiometabolic status of the patient (Table 1). Herein, we review the literature on cardiovascular (CV) risk in patients with CD, acromegaly, prolactinomas and hypopituitarism.

Table 1. Metabolic and cardiac structural and functional alterations in patients with GH deficiency, acromegaly, prolactinoma and CD.

	GHD	Acromegaly	Prolactinoma	Cushing's disease

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Lipid metabolism	Increased total cholesterol & LDL Increased triglycerides Decreased HDL	Increased lipoprotein Lp(a) Increased triglycerides Decreased HDL	Increased LDL Decreased HDL	Increased total cholesterol & LDL Increased triglycerides Decreased HDL
Cardiac structure and function changes	Diastolic dysfunction Myocardial hypokinesia Reduced left cardiac ventricular mass Low ejection fraction Compromised exercise capacity Hypertension	Left ventricular hypertrophy Systolic & diastolic dysfunction Cardiomyopathy Valvulopathies Hypertension	Subclinical cardiac dysfunction	Left ventricular hypertrophy Systolic & diastolic dysfunction
Insulin resistance/ metabolic syndrome	Obesity Increased subcutaneous and visceral fat Glucose intolerance	Reduced beta cell function Increased lipolysis Decreased glucose uptake Increased glycogenolysis & glyconeogenesis	Obesity Insulin resistance	Obesity Insulin resistance Diabetes mellitus
Endothelium and vasculature	Increased carotid intima media thickness Atherosclerosis of small and large vessels Reduced ascending aorta diameter	Endothelial dysfunction Increased endothelial proliferation Increased oxidative stress		
Coagulation abnormalities	Increased (PAI-1) Reduced protein S	Increased fibrinogen and (PAI-1) Decreased (t-PA) and (TFPI)		Hypercoagulability state
Pro-inflammatory markers and oxidative stress	Increased c-reactive protein Increased adipokines & pro-inflammatory cytokines (as IL-6 and TNF-α) Increased (PAPP-A) Elevated oxidated LDL	Increased proinflammatory cytokines Overexpression of cell adhesion molecules		Increased proinflammatory cytokines

Abbreviations: low-density lipoprotein (LDL), high-density lipoprotein (HDL), left ventricle hypertrophy (LVH), plasminogen activator inhibitor (PAI-1), pregnancy associated plasma protein A (PAPP-A), tissue plasminogen activator (t-PA), tissue factor pathway inhibitor (TFPI).

Cushing's Disease

Mortality

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CD is a rare condition of cortisol excess attributed to an ACTH secreting adenoma. Chronic hypercortisolemia is associated with cardiovascular abnormalities (visceral obesity, insulin resistance and impaired glucose tolerance, atherosclerosis, arterial hypertension, dyslipidaemia and hypercoagulability, structural and functional changes in heart) which do not seem to reverse completely even after remission. CV disease is the main cause of increased mortality which is observed not only in patients with persistent hypercortisolemia but also in those in remission [1–8].

A Danish study of 343 patients with Cushing's syndrome (CS) (211 patients with CD) estimated an increased risk for cardiovascular and thromboembolic events even 3 years before diagnosis. For the period 0-30 years after diagnosis the estimated hazard ratio risk (HR) for venous thromboembolism was 2.8 (95% CI 1.4-5.6), for acute myocardial infarction 3.6 (95% CI 2.2-5.9), for stroke 2.1 (95% CI 1.2-3.6) and for heart failure 1.3 (95% CI 0.5-3.2). Mortality risk was increased during first year and remained high during long term follow up and remarkably was higher in younger patients (≤44 years) than in older ones (HR 3.9, 95% CI 2.6-6.1 versus HR 2.0, 95% ci 1.5-2.6) [9]. A multinational, retrospective study from UK, Denmark, Netherlands, and New Zealand for patients cured from CD for a minimum of 10 years at study entry (320 patients) estimated an increased standard mortality ratio (SMR) for circulatory disease 2.72 (95% CI 1·88–3·95), while the overall SMR for all-cause mortality was 1.61 (95% CI 1·23–2·12) [2]. Recently a Swedish nationwide study including 502 patients with confirmed CD and median follow-up time 13 years, reported an increased SMR 6.9 (95% CI, 4.3-10.4) for patients not in remission and lower but still increased SMR for patients in remission 1.9 (95% CI, 1.5-2.3). CV disease was the commonest cause of death and CV SMR was 3.3 (95% CI, 2.6-4.3). More specifically, SMR for ischemic heart disease was 3.6 (95% CI, 2.5-5.1) and for cerebral infarction 3.0 (95% CI, 1.4- 5.7). For ischemic heart disease SMR for patients in remission was 2.7 (95% CI 1.7-4.2) for patients not in remission 10.7 (95% CI 3.5-25) while for patients with unknown remission status 10.4 (95% CI 4.2-22). These data highlight the irreversible negative effect of chronic hypercortisolemia on the CV and cerebrovascular system which contributes to an increased mortality even in cured patients [7].

The incidence of cardiac and cerebrovascular comorbidities has been investigated in 503 patients with CD during the period before diagnosis, from diagnosis to 1 year after remission, and during long-term remission. A 3-fold increased standard incidence ratio (SIR) was observed for stroke, 2-fold for myocardial infarction, 5-fold for pulmonary embolism and 3-fold for deep vein thrombosis. SIR for thromboembolism was increased in both the period before diagnosis 11.5 (95% CI 4.2- 25.0) and the peri- treatment period 18.3 (95% CI 7.9- 36). In particular, SIR for deep vein thrombosis was increased during both periods, while SIR for pulmonary embolism was elevated during the peri-treatment period. SIRs for myocardial infarction and ischemic heart disease, were increased only during the period of 3 years prior to diagnosis. SIR for stroke was increased (4.9, 95% CI, 1.3-12.5) during the peri-treatment period, but not before the diagnosis. SIRs for atrial fibrillation were also increased during the peri-treatment period. The incidence of stroke (3.1, 95% CI 1.8-4.9), and thromboembolism (4.9, 95% CI 2.6-8.4), remained elevated during long-term remission [10].

Metabolic Issues

Physiological Effects of Cortisol

Glucocorticoids (GCs) increase caloric and dietary fat intake [11]. They increase blood glucose levels by inhibiting peripheral glucose uptake by muscles and adipose tissue and by promoting gluconeogenesis and glycogenolysis in the liver. At the level of pancreas cortisol decreases insulin and increases glucagon, which enhances liver glycogenolysis, gluconeogenesis, ketogenesis and lipolysis and decreases lipogenesis. GCs increase de novo lipid production in hepatocytes and promote hydrolysis of circulating triglycerides (chylomicrons, very low-density lipoproteins) by lipoprotein lipase (LPL) activity and the conversion of preadipocyte to mature adipocytes. Accumulation of fatty acids in circulation results in ectopic fat distribution in the liver, muscle, and central adipocytes.

Effect of Cortisol Excess

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Obesity

Chronic hypercortisolemia has a negative effect on body composition. It increases the total and trunk fat and reduces the lean part [12]. A magnetic resonance study (MRI) study showed that females with active CD had significantly higher total, visceral and trunk subcutaneous adipose tissue, but similar intermuscular, despite lower skeletal mass, compared to weight matched controls [12]. Prolonged exposure to GCs suppresses the function of human brown adipose tissue (BAT) and favors energy production and lipogenesis [13]. Body composition changes remain impaired even after 5 years of remission and these patients have significantly higher body mass index (BMI) and waist-to-hip ratio (WHR) in comparison with age, sex and BMI matched controls [14]. An increased infiltration by CD68+ macrophages, CD4+ T lymphocytes, and CD11c+ macrophages and decreased vimentin characterizes the adipose tissue of patients with active CD compared with BMI-matched controls [15]. Excessive total and trunk fat and the inflammatory profile with low adiponectin and high TNF-1 and IL-6 persist even 11 years after remission of CD [16]. Similarly, proinflammatory IL-6 and IL-1β levels remained significantly elevated in a group of 31 patients with CD despite their remission (mean 19.5 months) and the significant decreases in their BMI, insulin resistance and visceral, hepatic and intermuscular fat stores [17]. TNF-1 has been associated with coronary calcifications in CD patients with long term remission (mean 11 years). Remission of CD for 6 months improves fat distribution and ameliorates but not completely the metabolic profile [18]. Persistent low-grade inflammation, contributes to the increased cardiovascular mortality in CD patients [19].

Glucose Metabolism

Hyperglycaemia in CD is due to several GCs-related actions [20]. GCs promote gluconeogenic enzymes and reduce insulin sensitivity in the liver and skeletal muscle. They increase proteolysis and subsequent muscle mass loss which results in impaired glucose uptake. They affect b-cell function interfering with glucose uptake and b-oxidation as well as with insulin secretion [21]. Abdominal obesity enhances insulin resistance and lipolysis, aberrant adipokine secretion, and low-grade inflammation. Amongst 25 patients with CD and 32 sex- and age-matched subjects (control-1 group) and 32 BMI-matched subjects (control-2), the prevalence of impaired glucose metabolism was higher in CD patients and recovered only in 2 patients (40%) after 1 year in remission [22]. Furthermore, patients with CD in remission for 5 years had higher fasting and stimulated glucose and insulin levels than sex- and age-matched controls. Diabetes mellitus was diagnosed in five patients (33.3%) and in two (6.7%) BMI- matched controls, whereas reduced glucose tolerance was found in four patients (26.7%), in three sex- and age-matched controls, and in eight BMI matched controls [14].

Lipid Metabolism

Excess GCs may lead to the development of dyslipidaemia due to the inhibition of LPL activity in adipose tissue. Patients with active CD have higher total, low density lipoprotein-cholesterol (LDL), total/high-density lipoprotein (HDL) ratio and lower HDL levels than sex and age matched (control-1) subjects and higher total/HDL ratio and lower HDL levels than BMI matched (control-2) subjects [23]. Markers of atherosclerosis as an increased intima-media thickness (IMT) and lower systolic lumen diameter and atherosclerotic plaques are more prevalent in comparison with either control group. One year after remission, although LDL-cholesterol and IMT significantly decreased and systolic lumen diameter significantly increased, they were still abnormal compared with sex and age matched controls but similar to BMI matched subjects [22]. Greater IMT has been estimated not only at carotid level but also at aortic sites in comparison with controls [23]. Coronary calcifications and/or noncalcified plaques have been demonstrated by noninvasive angiography in 42% of women and 30% of patients (<45 yrs) with long term remission (mean time 11.6 years) [22]. Echo doppler ultrasonography has showed that atheromatic indices remain impaired even after remission of 5 years [14].

Cardiovascular Issues

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Physiological Effects of Cortisol

GCs act through glucocorticoid and mineralocorticoid receptors on heart and blood vessels. Through different signaling pathways GCs are involved in angiogenesis, oxidative stress, and inflammation in vascular smooth and endothelial cells [24]. A well-recognized effect is the modulation of NO biosynthesis [25,26]. Systemic glucocorticoid administration in mice leads to hypertension through inhibition of NO metabolites and downregulation of the gene expression of NO synthase III in endothelial cells [27].

Effect of Cortisol Excess

Hypertension

Hypertension in CD is multifactorial and affects up to 81% of patients [28]. Underlying pathogenesis includes the activation of mineralocorticoid and glucocorticoid receptors, the upregulation of renin-angiotensin system and sympathetic nervous system and an imbalance between vasoconstriction and vasodilatation substances [29]. Electrocardiographic abnormalities with longer QTcd and shorter QTcmin, left and right ventricular hypertrophy (LVH), (RVH), higher systolic and diastolic blood pressure (SBP) are common [28].

CD patients exhibit greater degree of vasoconstriction and LV systolic dysfunction in comparison with hypertensive middle aged controls [30]. Lack of nocturnal blood pressure dipping was observed in 50% of patients with active disease and it remained 1 year after remission. Daytime heart rate was higher in active CD and decreased over time after cure [31]. In a group of 29 patients with CS (14 with CD) hypertension was demonstrated in 64% during the active period and 50% continued to need antihypertensive drugs 1 year after remission [32].

Structural and Functional Heart Disorders

During active CD impaired diastolic and systolic LV function has been detected [33] and 70% of patients with active CS present abnormal LV mass parameters; specifically concentric hypertrophy has been evaluated in 42% and concentric remodeling in 23% [34]. Even those with well controlled blood pressure (below 140/90mmHg) demonstrated significantly lower (LV) contractility and higher prevalence of LV diastolic dysfunction in comparison with hypertensive patients and healthy volunteers [30].

Thrombotic Risk

Hypercortisolism provokes a hypercoagulability state predisposing to venous and arterial thromboembolic events [35]. The underlying mechanisms include i) increase in pro-coagulation factors and shortened activated partial thromboplastin time (aPTT), (ii) impaired fibrinolysis, (iii) increased thrombin, thromboxane A2 and platelets, and (iv) compensatory increase in anticoagulation factors such as protein C and S. Endothelial dysfunction, increased IMT, vascular wall fibrosis and remodeling, increased vascular oxidative stress and atherosclerosis, obesity, hypertension, insulin resistance and diabetes contribute to disturbances in the hemostatic balance. The risk for venous thromboembolic events (VTE) after pituitary surgery is higher in CD patients (3.4%), in comparison with patients with nonfunctioning pituitary adenomas (NFPAs) (0%). The incidence rate for CD patients was 141 (95% CI 75–234) per 1000 person-years and the majority of events occurred between 1 week and 2 months after pituitary surgery. Medically pretreated patients had a lower risk of VTE in the 3 months after surgery (2.5%, 95% CI 1.2–5.1) compared with those who were not pretreated (7.2%, 95% CI 3.1– 15.9) [36]. A metanalysis of 2,083 cases undergoing either transsphenoidal (TSS) surgery (1476 cases) or adrenalectomy (607 cases) estimated that 4.75% (99/2,083) of patients had a VTE event within 30 days of surgery [37]. Postoperative reduction of cortisol activates inflammation and increases coagulation parameters and thrombotic risk and abnormalities persist up to 1 year or longer after remission. According to recent guidelines screening of cardiovascular risk and rigorous management should be performed during all stages of management of CD [38].

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Effects of Specific Treatments on Metabolic and Cardiovascular Issues

Treatment with levoketoconazole improves glycemic control in patients with DM [39]. Long term treatment with osilodrostat ameliorates metabolic and cardiovascular parameters and decreases weight, BMI, waist circumference, blood pressure, fasting plasma glucose, HbA1c, total cholesterol, and triglycerides [40]. Pasireotide therapy significantly reduces weight, BMI, waist circumference, as well as total and LDL-cholesterol, whereas significantly increases fasting plasma glucose and glycated haemoglobin [41,42]. Mifepristone is the only FDA-approved drug for glycaemia control in patients with Cushing's syndrome and type 2 diabetes. It enhances insulin-stimulated glucose uptake through a mechanism that involves a decrease in mitochondrial function and AMPK activation in skeletal muscle cells [43].

Acromegaly

Mortality

Acromegaly is characterized by increased levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) caused in the majority of cases by a GH-producing pituitary adenoma. Older studies reported increased SMR by 2-3 times, mainly due to CV and respiratory causes [44,45]. However, recent reports describe a reduction in SMR to levels similar to the general population with malignancies being the main cause of death [46,47]. SMR for all patients of the Swedish pituitary registry was 1.29 (95% CI 1.11-1.49). It was not increased in controlled acromegalics but it was elevated in non-controlled patients at the latest follow-up 1.90 (95% CI 1.33-2.72) (for the decade 1991-2000) and 1.98 (95% CI 1.24-3.14) (for the decade 2001-2011), respectively [48]. Both increased GH levels and duration of disease affect CV risk. Remarkably an average delay for diagnosis about 10 years has been estimated. The adoption of current, safe GH levels (random <1ng/ml, nadir during oral glucose tolerance test <0.4ng/ml) and age/gender normalized IGF-1 levels together with modern therapeutic modalities have improved patient outcomes [49].

Metabolic Issues

Physiological Effects of Growth Hormone

GH is acting as an anabolic hormone and induces lipolysis. This may occur by activation of hormone sensitive lipase (HSL) [50], a critical enzyme for lipolysis. GH inhibits LPL activity in adipose tissues, increasing serum lipids and changing body fat distribution. The increased availability of free fatty acids (FFA) in the context of insulin resistance increases triglyceride and reduces HDL levels [51]. Unlike in the adipose tissue, GH induces (FFA) uptake into skeletal muscle by up-regulation of LPL expression. The role of GH and IGF-1 in glucose metabolism is complex. GH promotes directly an insulin resistant state as it antagonizes insulin action and increases hepatic gluconeogenesis [52,53]. Moreover, it promotes triglyceride (TG) uptake into the liver by increasing (LPL) and/or hepatic lipase expression and/or activity. In addition, it stimulates TG secretion and hepatic fatty acid oxidation.

In the basal state, the effects of GH on protein metabolism are modest and include increased protein synthesis and decreased breakdown at the whole body level and in muscle together with decreased amino acid degradation/oxidation.

The Role of GH Excess

Obesity

No differences have been detected in body composition between controlled and not controlled acromegalics by the means of bioimpedance or dual-energy X-ray absorptiometry (DEXA) analysis [54,55]. Interestingly, a type of lipodystrophy with reduced adipose mass centrally and intrahepatic lipid and a shift of excess lipid to intramuscular adipose tissue has been observed [55]. The increased adipose content in muscle could be associated with GH-induced insulin-resistance [56]. GH directly promotes inflammation of human adipocytes by increasing VEGF and MCP1 levels [57].

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Glucose Metabolism

Chronic GH excess impairs insulin sensitivity, increases gluconeogenesis, reduces the glucose uptake in adipose tissue and muscle and alters pancreatic β-cell function. Hyperproinsulinaemia in acromegaly suggests that prolonged and excessive GH secretion may result in pancreatic β-cell dysfunction [58].

The prevalence of abnormal glucose tolerance is more than 50 % at the time of diagnosis and it is associated with an older age, a higher BMI, a family history of diabetes and a higher IGF-1 z-score, but not with fasting or post-OGTT GH levels [59]. The negative effect of diabetes in CV mortality of acromegalics was clearly demonstrated in the following Swedish, nationwide, study which compared 254 acromegalics with type 2 diabetes (ACRO-DM group) with 532 without diabetes (ACRO group) for a mean follow-up of 9.2 years. The unadjusted overall mortality rate per 1000 person-years was 35.1 (95% CI, 27.2-44.7) and 20.1 (95% CI, 16.5-24.3) respectively. HR for overall mortality was 1.58 (95% CI, 1.12-2.23), while CV mortality (HR 2.11; 95% CI, 1.09-4.10) and morbidity (HR 1.49; 95% CI, 1.21-1.82) were increased in the ACRO-DM group [60].

Lipid Metabolism

Acromegalic patients are characterized by lower HDL cholesterol and apoA-I levels and by higher triglycerides and Lp(a) concentrations in comparison to controls [61,62]. Additionally, they have increased levels of oxidative stress markers which contribute to a more atherogenic profile [63].

Cardiovascular Issues

Physiological Effects of GH

Under physiologic conditions GH and IGF-I are exerting a beneficial effect on CV system. GH and IGF-1 receptors are expressed in the heart and the vessels and regulate myocyte growth and structure, cardiac contractility and vascular function [64,65]. They affect peripheral resistance through the release of NO and/or other vasodilators from the endothelium or the regulation of gene expression of the vascular smooth muscle K-ATP channel. Aberrations in coagulation and fibrinolysis have been reported [66].

The Role of GH Excess

Hypertension

Hypertension is a major factor for CV mortality in acromegaly. Excess GH leads to increased sodium and water retention, by a direct kidney effect at the epithelial sodium channel (ENaC) subunit in the cortical collecting ducts [67]. The prevalence is estimated at approximately 30% and 50% of patients are non-dippers [68]. These changes are not always reversible and hypertension may persist in treated acromegalic patients [69,70].

Structural and Functional Heart Disorders

With normal GH/IGF-1 levels the protective PI3K-Act pathway predominates reducing vascular tone and oxidative damage. On the contrary, excess GH/IGF-1 levels acting through the MAPK pathway are leading to expression of pro-inflammatory cytokines and facilitate endothelial dysfunction and vascular remodeling [71].

Significantly lower flow mediated dilatation (FMD) of the brachial artery has been detected in acromegalics than in healthy and risk-factor-matched controls. Comparison of carotid IMT by ultrasonography showed no differences between acromegalics and controls and between active and controlled acromegalics [72]. 41% of acromegalic patients have evidence of coronary atherosclerosis and control of the disease does not influence the result [73]. Data from the German Acromegaly Registry estimated that SMR for myocardial infarction was 0.89, for stroke 1.17 and the latter was more increased in hypertensive patients [74].

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GH can stimulate cardiomyocyte hypertrophy independently of IGF-1 [65]. On the other hand, IGF-1 has a direct hypertrophic effect on cultured rat cardiomyocytes through its own receptor leading to increased actin/myosin expression, increased intracellular calcium levels and an anti-apoptotic effect [64]. However, the exact mechanism for the increased cardiac contractility and hypertrophy induced by excess GH/IGF-1 level remains unclear. In cardiac echocardiography studies, LVH ranges between 11-78% and diastolic dysfunction between 11-58% of patients [75]. Cardiac magnetic resonance (CMR) studies describe lower prevalence of LVH and development of myocardial fibrosis in 14.8% of patients [76].

Acromegaly is associated with a typical cardiomyopathy, characterized by biventricular hypertrophy, myocardial necrosis, lymphocytic infiltration, and interstitial fibrosis [68]. The first stage of cardiac hypertrophy presents as hyperkinetic syndrome with increased systolic output. At the intermediate stage, more severe hypertrophy is leading to diastolic dysfunction, in up to 58% of patients with active disease, and systolic dysfunction on effort. The end-stage is characterized by systolic dysfunction at rest and overt congestive heart failure (CHF). The progression to systolic dysfunction is generally uncommon (<3%) and CHF is rare in active acromegaly (1-4%). The 1- and 5-year mortality (or transplantation) rates for patients with chronic symptomatic CHF are 25% and 37.5%, respectively, as dilated cardiomyopathy is not reversible [77].

Cardiac arrhythmias, in the form of complex ventricular cardiac arrhythmias and sudden cardiac death are the most common causes of increased mortality in acromegaly. There are reports of elevated beat-to-beat QT variability and elevated late potentials. The low-amplitude, high-frequency waves in the terminal tract of QRS complexes correlate with ventricular tachyarrhythmias [45]. LV dyssynchrony is increased in acromegaly and may contribute to the progression to dilated heart failure [78]. Interstitial fibrosis is another factor that may cause arrhythmias in acromegaly since it disturbs the process of pulse propagation.

Valvulopathy has been reported, including mitral valve (5% vs 0% in controls) and aortic valve regurgitation (20% vs 4% in controls) with risk increasing by 19% per year with disease duration [79]. In a prospective study, mitral valve regurgitation increased from 46% to 76% in 2 years [80].

Thrombotic Risk

Abnormalities of hemostatic function include elevated levels of fibrinogen, antithrombin III, Plasminogen Activator Inhibitor-1 (PAI-1) and enhanced platelet activity and reduced levels of protein C, S and t-PA [66,81,82]. Moreover, patients with active acromegaly have disturbed fibrin network with more compact clots [83].

Effects of Specific Treatments on Metabolic and Cardiovascular Issues

Surgical treatment of acromegaly has a beneficial effect on insulin resistance and glucose metabolism [84], however, patients with already compromised β-cell function do not improve after surgery [85]. Somatostatin analogues (SSAs) improve insulin sensitivity but on the other hand inhibit insulin secretion [86]. In a prospective study SSAs as primary medical treatment for 5 years improved dyslipidemia and glucose tolerance was stable [87]. A recent meta-analysis showed that SSAs treatment in acromegaly patients, improve disease control, reduce insulin levels, and increase HbA1c levels without affecting fasting plasma glucose (FPG) [88]. Glucose monitoring is necessary during SSAs treatment, particularly for the second generation SSA pasireotide. Diabetes is diagnosed in up to 26% of patients who receive pasireotide both in responders and non-responders [89]. During long-term treatment with pegvisomant, fasting serum insulin and glucose levels decrease significantly [90]. Combination treatment of SSA and pegvisomant has a better effect on glucose profile compared with SSAs only [91]. Both surgery and SSAs have been reported to reduce triglycerides and increase HDL levels in acromegalic patients [87,92]. Pegvisomant increases significantly LDL and total cholesterol, whereas SSAs have no effect on LDL levels [93].

Modern management of acromegaly has reduced mortality and CV morbidities [94]. Hypertension responds to amiloride [95], but ACE-i or ARBs may also improve cardiac indices in

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CMR compared with other antihypertensive drugs [96]. Changes induced by GH excess may not be reversible and hypertension may persist in treated acromegalic patients [69,70].

The effect of GH/IGF-I excess on endothelial function is only partially reversible in cured acromegaly [70]. Patients with acromegaly have significantly impaired endothelial function as assessed by FMD, irrespective of disease activity [97]. In a prospective study where patients received 6 months SSAs, IMT had a trend only to decrease in patients with disease control [98]. Similarly, in another study a slight reduction of carotid arteries wall thickness and a significant improvement of brachial arteries vascular function was observed in patients with acromegaly resistant to SSA who were treated with pegvisomant [99].

Acromegaly cardiovascular disease improves after treatment by either surgery, SSA or pegvisomant. In a prospective study, LVM, LVMi, interventricular septum diastolic thickness (IVSDT) and posterior wall diastolic thickness (PWDT) were significantly reduced and diastolic function was significantly improved within 6 months after surgery [100]. The reversibility of LVH by SSAs appears by 3 months, and cardiac remodeling occurs quite quickly [77]. Reduction of LV mass correlates with the response to SSAs treatment [101]. SSAs have direct beneficial effects on cardiac myocytes and contribute to the improvement of echocardiographic parameters even in patients who have not achieved complete biochemical control of the disease [102]. Diastolic filling is improved, but the effect on ejection fraction and exercise tolerance is more variable. They have beneficial effects on cardiomyopathy that are not apparent in surgically treated patients [102]. The recovery of LV hypertrophy or diastolic and systolic dysfunction depends not only on the correction of hormone excess but also on patient age and disease duration [103]. In patients not controlled on SSAs alone, pegvisomant monotherapy [104] or in combination with SSAs [105] improves acromegalic cardiomyopathy.

Arrhythmias are ameliorated by SSAs therapy, possibly acting through the heart somatostatin receptors (SSTRs). SSAs have well-known electrophysiological properties like QT prolongation, early repolarization, low voltage, R/S transition, early R wave progression, and nonspecific ST-T wave changes, as well as bradycardia. In a cohort of acromegalic patients that presented >50 ectopic ventricular beats per 24h, a significant amelioration was observed after 6 months treatment with SSAs [106]. Attention is needed in patients that exhibit a prolonged QT interval, as risk of QT interval prolongation has been reported with pasireotide [107]. Some studies have shown no change in the frequency of ventricular arrhythmias after successful treatment of acromegaly, possibly due to the irreversibility of myocardial fibrosis in some cases. On the contrary, acromegalic patients that lacked structural heart disease had a low frequency of cardiac arrhythmias [108]. Pegvisomant has also been reported to improve arrhythmias [109]. 11- 30% of patients with acromegaly have obstructive sleep apnea (OSA), predisposing them to arrhythmias. The effect of acromegaly treatment on OSA is variable. However, despite cure of acromegaly, sleep apnea persisted in more than 40% of patients in prospective studies [110].

Of note, the incidence of valvular abnormalities and the risk for further progression of valvulopathy remain unchanged with treatment. Fortunately, data are reassuring regarding the risk for cardiac valve disease in patients with acromegaly treated with cabergoline [111].

The disturbed parameters of coagulation and fibrinolysis have been considered to contribute to the increased cardiovascular risk in acromegaly. Some of these abnormalities are reversible after surgical or medical treatment. Fibrinogen levels are reduced in controlled patients [98] and platelet volume and function are at least partially normalized [112]. Similarly, the abnormal clot structure properties in active acromegaly seem to ameliorate in patients with long term disease remission [83].

Real world data show that comorbidities are less prevalent in controlled patients, but unfortunately a third of the patients remained uncontrolled after 8 years of treatment which demonstrates the difficulty of achieving control in some patients [113].

Prolactinomas

Mortality

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CVD related mortality is lower in prolactinomas compared to ACTH, TSH and NFPA patients. In a study from Korea SIR for hemorrhagic stroke was 3.88, for ischemic stroke 2.94, while for acute myocardial infarct was 1.94 [114]. Higher incidence rate of cardiovascular events has been estimated in males (14.8 per 1000 person-years versus 1.8 for the females [115].

Metabolic Issues

Physiological Effects of Prolactin

Prolactin and dopamine receptors type 2 are expressed on both human pancreatic β- cell and adipocytes, supporting a key role of prolactin and dopamine in peripheral metabolic regulation. PRL excess is known to influence the orexigenic–anorexigenic systems that regulate appetite and elicits an increase in food intake, leading to weight gain and obesity [116].

The Role of Prolactin Excess

Obesity

In comparison with the National Health and Nutrition Examination Survey population, patients with prolactinomas and particularly men have an increased prevalence of class II obesity [117]. They have significantly higher BMI than controls; but fat mass is higher only in men [118]. Weight gain is a presenting feature in prolactinoma patients and normalization of prolactin with either transsphenoidal surgery (TSS) or dopamine agonists (DA) is associated with weight loss and BMI reduction [119,120]. Treatment with cabergoline decreases significantly the visceral adiposity index [109].

Glucose Metabolism

Data for glucose metabolism are not consistent and either higher fasting glucose levels [83] or similar to controls [118] have been observed. Dopamine agonists improve insulin sensitivity [120,121]. This effect happens independently of prolactin decrease [122]. Decrease of fasting glucose has been observed after normalization of prolactin with either TSS or DA therapy [123].

Lipid Metabolism

Patients with prolactinoma have higher levels of LDL and lower levels of HDL in comparison with controls. Treatment with dopamine agonists decrease LDL levels [120,121].

Cardiovascular Issues

Physiological Effects of Prolactin

Prolactin may act on ventricular myocyte [124]. It exerts a direct inotropic positive action on the mammalian myocardium, partly mediated via the local release of catecholamines and the cAMP pathway [125].

The Role of Prolactin Excess

Hyperprolactinemia in humans may be associated with a slight impairment of diastolic function [126]. Epicardial adipose tissue thickness (EATT) is a surrogate marker for visceral fat and a novel cardiovascular risk indicator. EATT and cIMT are greater in patients with prolactinoma, despite their normal cardiac systolic and diastolic functions [127,128]. Subclinical cardiac dysfunction has been observed in untreated patients and is characterized by impaired LV systolic and diastolic function, as well as regional segment motional abnormality [87]. Treatment with cabergoline improves inflammatory markers and decreases cIMT independently from the decrease in prolactin, LDL cholesterol and BMI [122].

Effects of Specific Treatments on Metabolic and Cardiovascular Issues

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Cabergoline improves insulin sensitivity and inflammatory markers and causes a decrease in CIMT independently of the decrease in prolactin, LDL cholesterol and BMI [122]. Major adverse effects that should be monitored during treatment with dopamine agonists consist of cardiac valvulopathy and impulse control disorders[129,130].

Hypopituitarism

Mortality in Hypopituitary Patients

Patients with pituitary deficiency consist an heterogenous group, due to the variable severity of the disease, ranging from isolated deficiency of one hormone to multiple hormone deficiencies. As CVR depends on numerous factors apart from pituitary deficiency (vessel and heart diseases, lipid and coagulation abnormalities, family history, sex, smoking, obesity), mortality may vary greatly in hypopituitarism.

The great interest about CVR and pituitary deficiency started in early 1990's, when Rosen & Bengtsson [131] published on premature mortality from cardiovascular disease in these patients. As evidence grew, it became apparent that women with pituitary deficiency suffered more often than men [132]. Apart from sex, age at the onset of hypopituitarism was identified as an important determinant of CVR. Young age, both in men and women, has been associated with an increased HR for CVR [133]. Additionally, the cause of hypopituitarism is a determinant of CVR, as for example, craniopharyngiomas exhibit much higher cardiovascular mortality than non-functioning adenomas [134]. Moreover, treatment modalities may contribute to CVR, for example; a) the treatment itself, with the example of radiotherapy and vascular deaths and b) the fact that multiple treatments may cause more often pan-hypopituitarism that is known to augment CVR [135]

GH deficiency was implicated as the main cause for CVR mortality, given the fact that hypopituitary patients were treated conventionally with thyroxine, cortisol and gonadal steroids when needed, but no GH [136].

The conventional hormone replacement in hypopituitary patients has been considered far from ideal. It has been gradually understood that the conventional glucocorticoid replacement was actually an over-treatment. That chronic, albeit mild, exposure to elevated glucocorticoids has been associated with glucose intolerance, hypertension, obesity and hyperlipidemia [137] and cardiovascular morbidities a) atherosclerosis and increased vessel resistance, b) systolic and diastolic heart dysfunction and c) impaired heart contractibility [138].

Growth Hormone Deficiency

GH Deficiency and Metabolism

Adult patients with GH deficiency are often obese. The excess body fat is mostly abdominal as it is estimated by an increased WHR and consists not only of subcutaneous, but also of visceral fat. The latter is associated with insulin resistance and type II diabetes [139].

An increased prevalence of metabolic syndrome by 20-50% compared to the general population is observed in patients with hypopituitarism [140,141]. The risk is higher in female GH deficient patients, those with adult-onset disease and patients older than 40 years [142].

GH deficiency is associated with raised total and LDL-cholesterol and triglycerides and decreased levels of high-density lipoprotein (HDL). HDL abnormalities are more frequent in females [143,144]. Lower concentrations of apolipoprotein A1 and higher levels of apolipoprotein B have also been reported [136], adding to the unfavorable profile in GH deficient patients.

GH Deficiency and Cardiovascular System

Hypopituitary patients suffer from atherosclerosis of small and larger vessels [145]. An increased IMT in carotid arteries [146,147] has been detected. Patients with GH deficiency exhibit decreased fibrinolysis, primarily due to increases in PAI-1 [148]. Moreover, they have endothelial dysfunction due to increased levels of C-reactive protein, adipokines and pro-inflammatory cytokines (as IL-6 and TNF-α) [149].

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GH deficiency is related with structural and functional cardiac abnormalities which lead to diastolic dysfunction and myocardial hypokinesia. The left cardiac ventricular mass is often reduced and patients may have low cardiac output and ejection fraction and subsequently a compromised exercise capacity. A metanalysis of cardiac MRI studies have confirmed the ventricular alterations both in the right and left ventricle of these patients [150].

GH replacement may improve numerous parameters of cardiac structure. In addition to the increase of ejection fraction and decrease of NT-BNP, it ameliorates the systolic function in adult patients [151].

Secondary Cortisol Deficiency

Cortisol Deficiency and Metabolism

Cortisol excess is associated with central fat accumulation [152]. However, patients with secondary cortisol deficiency may also be obese. Secondary cortisol insufficiency occurs late in the events of hypopituitarism and its effect on body composition and metabolism are intermixed with the effects of other anterior pituitary hormone deficiencies. As a result, the weight loss that is observed in primary adrenal insufficiency may not be present in secondary cortisol deficiency. Treatment of these patients, especially with dual release hydrocortisone induces reductions in BMI and waist circumference [153].

Cortisol affects glucose homeostasis by inducing insulin resistance and hyperglycemia [154]. The most striking symptom of cortisol deficiency is hypoglycemia, which disappears after cortisol substitution. In cortisol deficiency raised triglycerides, low-HDL cholesterol and increased CRP contribute to the increased cardiovascular risk, although variations exist in lipid levels due to genetic and environmental factors [155].

Cortisol Deficiency and Cardiovascular System

The human heart and vessels express glucocorticoid receptors and cortisol has an important role in cardiovascular function. Cortisol deficiency affects myocardial contractibility [156]. Reports on secondary adrenal insufficiency and coagulation are scanty: studies reporting bleeding or thrombotic events is lacking. Patients with Sheehan's syndrome demonstrate thrombocytopenia, shorter PT and aPTT and von Willenbrand factor deficiency [157].

Gonadotrophin Deficiency

Gonadotrophin Deficiency and Metabolism

Gonadal steroids affect body composition and intermediate metabolism. Low testosterone increases body fat mass and is associated with insulin resistance, metabolic syndrome, type II diabetes and obesity [158]. The lipid profile associated with low testosterone is atherogenic, with increased total, LDL cholesterol and triglycerides [159] and low HDL cholesterol and apolipoprotein A [160]. Low estradiol levels in menopause and hypogonadism are associated with an increase of total and central body fat and reduced insulin sensitivity. Elevated LDL cholesterol occurs frequently, although the lipid derangements of the metabolic syndrome are also observed [161].

Gonadotrophin Deficiency and Cardiovascular System

Hypogonadal untreated patients have increased mortality [134] due to cardiovascular morbidities. Low testosterone correlates with heart failure severity [162]. Nevertheless, some data on testosterone replacement in hypogonadal men also demonstrated an increase in CV events [163].

Cardioprotection in women is lost in menopause as estrogen deplete and diastolic dysfunction, cardiac hypertrophy, ventricular stiffness and heart failure may appear [164].

Thyrotropin Deficiency

Central Hypothyroidism and Metabolism

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Thyroid hormones induce thermogenesis and increase energy expenditure. They regulate basal metabolic rate and influence body weight. Hypothyroidism may result in obesity although weight loss after treatment of hypothyroidism is mainly related to excretion of excess body water [165].

A complex interplay exists between thyroid hormones and body composition, glucose and lipid metabolism [166]. Hypothyroidism has been associated with insulin resistance and current studies indicate a higher risk for type II diabetes in these patients [167,168].

Thyroid hormones regulate lipid metabolism, primarily via liver dependent effects and multiple mechanisms. The induction of cholesterol uptake through activation of LDL-receptor genes is a significant pathway. However, reductions in apolipoproteins, namely apo-B48 and apo-B11 may additionally decrease LDL-cholesterol [169].

Central Hypothyroidism and Cardiovascular System

Thyroid hormones play a significant role in the control of systolic and diastolic blood pressure, due to their effects on peripheral vascular resistance and arterial stiffness [170]. The endothelial NO production is also regulated by thyroid hormones and affects vascular tone. An atherogenic profile is seen in hypothyroidism with hypercholesterolemia with increased levels of CRP, homocysteine and PAI-1. Hypothyroidism carries an increased risk of hypertension and atherosclerosis [171].

The renin-angiotensin-aldosterone system is downregulated in hypothyroidism, as well as the beta-adrenergic system in cardiomyocytes. Therefore, in untreated hypothyroidism bradycardia, reduced heart contractibility, narrowed pulse pressure and low cardiac output can be seen [171].

Posterior Pituitary and CVR

The presence of diabetes insipidus and chronic mild hypo-hydration may also exhibit increased cardiovascular disease risk [172].

Conclusions

Cardiovascular comorbidities are the main contributor to the increased mortality of patients with pituitary disorders and especially in those suffering from CD, acromegaly and hypopituitarism. Acromegaly, GH deficiency, Cushing syndrome, and chronic glucocorticoid replacement are associated with increased atherosclerotic cardiovascular risk. Pituitary hormonal excess or deficiencies contribute to detrimental alterations in glucose and lipid metabolism, endothelial function, body composition and heart structural and functional disorders. Early diagnosis and successful management is challenging but may normalize the cardiovascular burden of disease.

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