Suggestion to add Cushing’s syndrome to the list of the diseases with high cardiovascular risk in relevant guidelines

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Abstract:
The aim of the paper is to give rationale and to propose listing Cushing’s syndrome among high CV risk conditions. Respectable amount of published data points to several-fold enhanced mortality in Cushing’s syndrome. Reasons are high prevalence of numerous cardiovascular risk factors in Cushing’s syndrome, such as arterial hypertension, diabetes mellitus, dyslipidemia, obesity. Consequently, virtually all patients with Cushing’s syndrome have also the metabolic syndrome, which is recognized as loaded with high cardiovascular risk. Specifically, despite the young mean age, 80% of CS patients presented a 'high' or a 'very high' CV risk, a > 20% risk of a major CV event within the next 10 years. Hypertension-induced target organ damage, including left ventricular hypertrophy and retinopathy, are frequently found in Cushing’s syndrome, adding to the global cardiovascular risk. Moreover, diabetes mellitus is listed as high risk condition, but Cushing’s syndrome (with majority of patients having either diabetes mellitus or impaired glucose tolerance) is not. In recent guidelines Cushing’s syndrome is mentioned as a risk factor for aortic dissection, and it should be also cited as a disease with high cardiovascular risk (like diabetes mellitus and chronic renal failure) in the pertinent guidelines.

Key-Words: Cushing’s syndrome, cardiovascular risk factors, arterial hypertension, diabetes mellitus, dyslipidemia

1 Introduction
Cushing’s syndrome (CS) is a group of diseases, which result from the prolonged excess of glucocorticoid hormones. CS can be endogenous or exogenous. Endogenous CS are adrenocorticotropic hormone (ACTH) -dependent types of CS: pituitary adenoma (Cushing’s disease, 70%) and ACTH overproduction from tumor (10%), while ACTH-independent causes are adenoma (10%) and cancer (5%) of the adrenal gland which both increase secretion of cortisol [1]. Exogenous (mainly iatrogenic), is the consequence of the administration of glucocorticoids or ACTH. Iatrogenic CS is today by far the most common form of all types of CS. Namely, as many as 1% of the population is taking oral corticosteroids (even 3% of persons over 70 years), plus patients who use other routes - inhaled, creams, intravenous, intramuscular, intraarticular, rectal, etc) [2]. In patients with CS we should be particularly careful in identifying global cardiovascular (CV) risk and aim at controlling all comorbidities, including the follow-up after cortisol normalization [3].

2 Problem Formulation
CS is listed in 2010 Guidelines as RF for aortic dissection without detailed explanation [4]. Therefore, what is obvious both from common medical sense and from everyday practice (that CS should be regarded as a sort of high CV risk) is not in Guidelines; however, what is neither evident, nor frequent (that CS patients are prone to aortic dissection) is a part of Guidelines [4]. The aim of the paper is to give rationale (from available medical literature) and to propose listing CS among high CV risk conditions.

3 Problem Solution
The arguments to cite CS as a high-risk condition are the following.

3.1 Mortality data
Inadequately treated CS patients may have mortality of 50% in 5 years [5], [6]. CV
complications in patients with CS cause a mortality rate of fourfold higher than expected [7]. Patients with persistent hypercortisolism after treatment continue to have a 3.8-5.0-fold increased standard mortality ratio when compared to the general population, but with an effective therapy, the standard mortality ratio becomes similar to age-matched populations [8]. Absolute risk of major CV events can be estimated by considering the combinations of: 1. risk factors (RFs) (HTN, DM, etc), 2. organ damage (left ventricular hypertrophy/LVH, proteinuria, etc) and 3. associated diseases (heart failure, etc) [9].

The most important RFs for atherosclerosis including CAD are: HTN, dyslipidemia, DM, smoking, obesity, physical inactivity, psychosocial factors, genetic factors, and renal impairment [10], [11], [12]. In CS, the main vascular alteration is atherosclerosis [7]. Target organ damages (TODs) make the prognosis in HTN worse [13] and ≈80% CS patients have HTN. Chronic cortisol hypersecretion causes central obesity, HTN, insulin resistance and DM, dyslipidemia and protrombotic state, manifestations which form a MetSy virtually in every patient with CS [14]. The central features of the MetSy were described >80 years ago as HTN, hyperglycemia and gout [15]. Reaven (1988) proposed the name “syndrome X”, in which a cluster of metabolic disorders [such as impaired glucose tolerance (IGT), dyslipidemia, obesity, and HTN] causes a variety of vascular disorders. The concept of the “multiple RF syndrome” (also previously named deadly quartet, insulin resistance syndrome, and visceral obesity syndrome), has recently been standardized as “the MetSy” [16]. Accordingly, almost all traditional CV RFs that constitute MetSy are usually found in overt CS: obesity, DM, HTA, HLP, etc.

3.2 Obesity
The centripetal obesity of CS results in disproportionate weight gain in the abdomen [17]. Prevalence of obesity or overweight is 80% in CS [2]. Duration of CS correlated with the presence of obesity and HTN [18].

3.3 Hypertension
HTN is very important medical and social problem, e.g. suboptimal blood pressure (BP) (systolic BP >115mmHg) is responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease in those aged 40 to 89 years [19]. HTN is a hallmark of CS, present in most patients with CS (70–90%) and has deleterious consequences, so much so that Harvey Cushing himself, in 1932, noted that out of his first 12 patients 9 suffered from HTN [9]. In iatrogenic CS, HTN prevalence is much lower (<20%), the risks are lower and proportional to the dose and duration of glucocorticoid therapy [17], [19], [20], [21]. HTN is present in 50% in children and adolescents with CS [22]. Severe HTN has been described in 17% of CS patients. TODs are more severe in CS than in primary HTN [23]. CS may cause resistant AHT, with higher potential for TODs [8], [23], [24]. In CS patients that entered remission, the prevalence of HTA remained high (>57%) [25]. However, 12 months following surgical cure of CS, systolic BP remained increased in only 5.5% of hypertensive children and adolescents, and diastolic BP was completely normalized after 3 months [6]. In CS HTN may result from combination of factors: (a) increased circulating levels of angiotensin II due to the increase of hepatic angiotensinogen synthesis; (b) increased reactivity to vasoconstricting stimuli of angiotensin II, catecholamines, vasopressin, etc. (c) inhibition of vasodilatory systems such as nitric oxide (NO), kinin/ kallkrein, prostacyclin; (d) inhibition of peripheral catabolism of catecholamine, in particular of norepinephrine; (e) direct action of glucocorticoids on CV receptors; (f) increased calcium uptake in vascular smooth muscle cells; (g) decreased vasodilatation by atrial natriuretic peptide (ANP) [9], [17], [26]. Additionally, hypertrophic remodeling of small resistance arteries occurs in CS in a pattern distinct from the eutrophic remodeling seen with essential HTN or catecholamine excess [17]. Besides, disproportionate weight gain in the abdomen, neck, and head is associated with sleep apnea, which can cause / worsen HTN [17]. Furthermore, endothelin system is activated in CS [27], the serum EPO concentration is increased and changes in BP correlate with changes in EPO. AHT in CS is well recognized secondary and endocrine HTN. It is even considered „surgical AHT“, because CS represents <1% of AHT patients who get operated to cure AHT.

3.4 Diabetes mellitus
The liver is a major target organ of glucocorticoids, which activate hepatic glucose-6-phosphatase and phosphoenolpyruvate kinase increasing gluconeogenesis. Glucose uptake and use in muscle and fat are inhibited. Glucocorticoids also potentiate the effects of catecholamines and glucagon. The net result is: insulin resistance, hyperglycemia, and increased CV risks [17]. IGT or type 2 DM occurs in ~80% of patients with CS [28]. In >2/3 of the CS patients DM was diagnosed by oral glucose tolerance test (OGTT), indicating that fasting glycemia alone underestimates the prevalence of
DM in CS [9]. Fasting plasma glucose rose consistently already after 5 days of glucocorticoid treatment [14]. IGT persists years after cure of the underlying disease in the setting of CS [1]. Elevated insulin persists 5 years after the effective treatment of Cushing’s disease [14].

3.5 Dyslipidemia
Glucocorticoids increase lipolysis in adipose tissues and lipoprotein synthesis in the liver. With prolonged exposure, circulating cholesterol and triglycerides rise, and the high-density lipoprotein / low-density lipoprotein (HDL / LDL) ratio is reduced [17]. In addition, cortisol directly inhibits pituitary TSH secretion, resulting in hypothyroidism [17]. Glucocorticoid -induced (“steroid”) DM additionally worsens dyslipidemia. Combination of the humoral factors related to the MetSy, including the adipokines, synergistically enhances the hepatic expression of 11β-HSD1 gene and causes the intracellular Cushing state in the liver - by increasing the intracellular glucocorticoid level [16].

There is no reason to believe that CS patients smoke less then others. CS patients might have even higher prevalence of smoking. Namely, exogenous (iatrogenic) CS might be the result of administration of glucocorticoids for a neoplasm or chronic obstructive lung disease (for which smoking is a RF).

Insufficient exercise can be reasonably expected in higher percentage among CS patients. Specifically, CS patients per se, especially those with pituitary or adrenal tumor are less likely to exercise, because of obesity, fatigue, psychical problems, etc. Over 80% of CS patients have symptoms consistent with an episode of major depression [8]. Moreover, numerous diseases - which require glucocorticoid treatment - are severe, as a rule (e.g. lymphoma, rheumatoid arthritis, etc), precluding regular exercise. Indeed, there is no definitive evidence for increased smoking prevalence and lack of physical activity in CS patients.

CV risk increases substantially with raising number of RFs and patients with overt CS typically have more of them: ≥60% of patients had ≥3 CV RFs [9]. Despite the young mean age, 80% of CS patients presented a 'high' or a 'very high' CV risk, a > 20% risk of a major CV event within the next 10 years [18] and over a 20% risk of experiencing a CV event before the age of 50 [9].

Regarding organ damage in CS, 2/3 of patients presented HTN complicated by LVH and retinopathy. Length of CS correlates with the presence of HTN and obesity, being the only significant and independent predictor of CV risk [9].

The persistence of a MetSy, vascular damage, and atherosclerotic plaques, keeps CS patients still at high CV risk up to 5 years after resolution of hypercortisolism [14], [29]. As subclinical CS and MetSy share many clinical features (obesity, dyslipidemia, HTN, IGT), there are considerable difficulties to differentiate between them [30], illustrated by the title: “Is MetSy a mild form of CS?” [31]. There are many additional evidences for the increased CV risk in CS. For example, in 22-32% of CS patients hypokalemia can be found [21], which is well recognized arrhythmogenic factor, and may lead even to fatal ventricular arrhythmias. Approximately 80% of patients with CS have an increased albumin excretion in the urine, 61.5% have microalbuminuria [1]. Endothelial dysfunction may develop in the preclinical phase of vascular disease in patients with CS [32]. Carotid intima-media thickness is increased in CS [1], [7].

Glucocorticoid excess in CS results in a hypercoagulable state, which increases four-fold the incidence of pulmonary embolism, deep vein thrombosis, and mortality [33], [34], [35]. About 10% of patients with CS have serious thromboembolic complications, especially after surgery or after inferior petrosal sinus sampling. Glucocorticoids increase the synthesis of many coagulation factors [9], thrombin and plasmin [17]. Hypercoagulability in CS is manifested as increased prothrombotic activity and compensatory activation of the fibrinolytic system. Thromboprophylaxis in the preoperative and early postoperative periods is suggested, combined with a close follow-up [36]. Moreover, polycythemia is a well-recognized complication of chronic glucocorticoid excess and it is thrombogenic [37]. Additionally, hyperhomocysteaemia (which is thrombophylic) and reduced serum folate concentrations are present in active CS, and they return to normal during remission [17], [38], [39].

In addition, cardiac hypertrophy is a common finding, even in the absence of HTN. The LVH is more severe in CS than in essential and other secondary HTN, and can regress dramatically after CS treatment [40]. Patients with CS have impaired systolic function as well as cardiac hypertrophy, which correlate with the duration of cortisol excess, suggesting that cortisol excess per se may play a significant role [40], [41]. A characteristic alteration of cardiac structure is found in CS - high relative wall thickness (which was not related to BP levels),
reduced midwall systolic performance and diastolic dysfunction. They may contribute to the high risk of CV events observed in CS [41]. Ma et al. proposed that cardiac dysfunction in CS might be a manifestation of lipotoxic heart disease [40]. ECG, 24h ambulatory BP monitoring, echocardiography, OGTT and carotid artery ultrasonography are suggested for CS patients [7]. Glucocorticoids are immunosuppressive agents and increase susceptibility to infections. Infections may contribute in ACS pathogenesis.

Prevalence of subclinical CS (when clinical picture is not recognizable) is much higher than that of overt CS and progression to full-blown CS occurs in 12.5% per year. As subclinical CS (subclinical hypercortisolism) has an increased risk of CV morbidity and mortality [28], [42], it is clear that patients with full-blown CS (when clinical picture is typical) are at much higher risk. Wei et al. analyzed no less than 68,781 glucocorticoid users and 82,202 nonusers without previous hospitalization for CV disease (>150,000 persons in total). After adjustment for known covariates, the relative risk for a CV event in patients receiving high-dose glucocorticoids was 2.56 (CI, 2.18 to 2.99) [43]. This population-based study shows that patients who were exposed to dosages of glucocorticoids greater than the equivalent of 7.5 mg of prednisolone per day during 1 to 5 years of follow-up had substantially higher rates of all CV diseases, including myocardial infarction, heart failure, and cerebrovascular disease [43].

Considering that remission from hypercortisolism is often difficult to achieve, especially in pituitary forms, and that CV risk can persist even during disease remission, care and control of all CV RFs should be one of the primary goals [9]. Hence, patients with CS are at high risk for CV events, but surprisingly, none of the 9 relevant guidelines mentioned it. [10], [11], [12], [13], [19], [44], [45], [46], [47].

4 Conclusion

1. Being witnesses of pandemic obesity, doctors should both do their best to treat metabolic syndrome and be vigilant enough to notice subtle signs of Cushing’s syndrome in some of them.
2. Great number of case reports presenting Cushing’s syndrome following seemingly low dose and/or short term (even topical) glucocorticoid therapy should instruct us to check up possible physical signs and laboratory markers of new-onset Cushing’s syndrome more actively and regularly. It is especially true for patients who receive some other (of the numerous) drugs which are metabolized by CYP 3A4.
3. DM is is listed as a high risk condition, but Cushing’s syndrome (with majority of patients having either DM or IGT) is not.
4. Additional argument to record Cushing’s syndrome among conditions with high cardiovascular risk is that virtually all patients with Cushing’s syndrome have also the metabolic syndrome, which is recognized as loaded with high cardiovascular risk.
5. Moreover, there are direct evidences of high risk: mortality is increased several-fold in Cushing’s syndrome, particularly if glucocorticoid excess can not be completely cured.
6. Cushing’s syndrome is mentioned as a risk factor for aortic dissection in recent guidelines, and it should be also cited as a disease with high cardiovascular risk (like DM and chronic renal failure) in other guidelines.
7. When Harvey Cushing described his syndrome in 1932 he named it the killing disease because of its cardiovascular complications. With so much evidence and consistently with common medical sense, the time has probably come for us to put Cushing’s syndrome (especially if glucocorticoid excess can not be eliminated) on list of diseases with high cardiovascular risk in relevant guidelines.

References:


