FACTA UNIVERSITATIS
Series: **Medicine and Biology** Vol. 24, No 2, 2022, pp. 51–55

UDC 616.453:616.12-2-085
https://doi.org/10.22190/FUMB210130007K

Review Article

A SUGGESTION FOR PROACTIVE CARDIOLOGIC APPROACH TO CUSHING'S SYNDROME OR DISEASE

Goran Koraćević[1,2], Miloš Zdravković[2], Maja Koraćević[2], Dimitrije A. Pavlović[3], Miodrag Damjanović[1], Milorad Pavlović[4], Sonja Dakić[1], Predrag Cvetković[1], Katarina Mladenović[5], Milan Stojković[6]

[1]Depatment for Cardiovascular Disease, University Clinical Center Niš, Serbia
[2]Faculty of Medicine, University of Niš, Serbia
[3]Department of Plastic and Reconstructive Surgery, University Clinical Center Niš, Serbia
[4]Department of Thoracic Surgery, University Clinical Center Niš, Serbia
[5]Faculty of Science, Department of Biology and Ecology, University of Kragujevac, Serbia
[6]Department of Internal Medicine and Geriatrics, Bethel Clinic (EvKB), Bielefeld, Germany

Abstract. *Numerous studies and reviews agree about the increased cardiovascular risk in Cushing's syn-drome. Therefore, the aim of the paper is to suggest a few common diagnostic and therapeutic cardiologic preferences for the majority of Cushing's syndrome/Cushing's disease (CS/CD) pa-tients which are not yet routine but have the rationale to become standard procedures. This may serve as an initial working document, to be improved by the experts in the field. A narrative review is used to present synthesis and deduction of several approaches in cardiology regarding the actu-al topic. Results are systematized as the risk factors or co-morbidities list (prevalent in CS/CD) coupled with current and adapted cardiologic suggestions for practice.*

Key words: *Cushing's syndrome, Cushing's disease, ACE inhibitor, spironolactone, statin, holter monitoring*

Introduction

Cushing's syndrome (CS) is important due to the high prevalence [1] of its exogenous (mostly iatrogenic) form [2,3]. Numerous comorbidities are often present in CS / Cushing's disease (CS/CD) [4,5]. The mortality rates are increased in CS/CD [4,6] in the range between 1.8 and 7.4-fold higher [5]. Numerous studies and reviews agree about the increased cardiovascular risk in CS/CD [2,4-6]. Cardiovascular risks ought to be repeatedly estimated in clinical practice and care should be taken to control them optimally, because they are pronounced and persistent -it is not easy to eliminate hypercortisolism and even if it is achieved- cardiovascular risk factors may still be present [7].

Unfortunately, abundant evidence of high cardiovascular risk in CS/CD is sub-optimally translated into practical recommendations [5]. There is a step between recognizing increased risk in the medical literature and incorporating this knowledge into the physicians' usual care for the patient. The cardiologic part of such interdisciplinary recommendations (endocrinologic and cardiologic) is largely missing [5].

Therefore, the *aim* of the paper is to suggest a few common diagnostic and therapeutic cardiologic preferences for the majority of CS/CD patients which are not yet routine but have the rationale to become standard procedures. This may serve as an initial working document, to be improved by the experts in the field.

Correspondence to: Miloš Zdravković
Faculty of Medicine, University of Niš;
Address for correspondence: Dubočica 107B/6, 16000 Leskovac, Serbia
E-mail: zdravkovicmilos@outlook.com
Received January 30th, 2021 / Accepted October 11th, 2022

Materials and Methods

A narrative review is used to present the synthesis and deduction of several approaches in cardiology regarding the actual topic. We performed a search in the following databases: Medline, Springer, Elsevier, SAGE, Oxford Press, Wiley, and the search engine Google Scholar. Results are systematized as the risk factors or co-morbidities list (prevalent in CS/CD) coupled with current and adapted cardiologic suggestions for practice.

Results

Arterial hypertension (HTN) (Table 1) is very prevalent in CS/CD in the range of 70% to 90% [6,5]. Blood pressure (BP) may increase early in CS/CD. For example, HTN starts during the first day of oral intake of 80 mg – 200 mg cortisol daily and peak BP increase occurs after 4 or 5 days [8]. Ambulatory BP monitoring (ABPM) is now very important for HTN detection and evaluation [9-11]. ABPM can be recommended for many CS/CD patients, particularly if long-standing and/or severe [12]. Importantly, ABPM can be used to detect masked arterial hypertension (MAHT) [9-11] in CS/CD patients because

they have numerous characteristics associated with MAHT [12]. Additionally, there is a place of ABPM in CS/CD patients with sustained HTN – to evaluate antihypertensive therapy [9].

Obesity and DM increase the likelihood of uncontrolled or masked uncontrolled HTN (MUCH) [9] and they are features of CS/CD [5]. Moreover, in CS/CD there is often persistent hypercortisolism, which promotes HTN [7]. In the pathophysiology of HTN in CS/CD numerous factors play a role: obesity, elevated cardiac output, activation of the renin-angiotensin-aldosterone system (RAAS), increased cardiovascular sensitivity to vasopressin, angiotensin II and catecholamines, reduced efficacy of vasodilatory mechanisms, higher total peripheral vascular resistance, mineralocorticoid action of cortisol and mineralocorticoid hormones co-secretion (e.g., deoxycorticosterone), sleep apnoea, etc[5,7,8,13-15].

RAAS blocker (ACE inhibitor or angiotensin receptor blocker (ARB)) is one of the first choices for HTN treatment in CS/CD [15,16]. RAAS blocker is generally a part of the preferred combination to start antihypertensive therapy with [9] RAAS blocker is also indicated in obese HTN patients [9] and most of the patients with CS/CD are obese [5].

In addition to the RAAS blocker, a direct suggestion for antihypertensive therapy in CS/CD patients is a *mineralocorticoid receptor antagonist (MRA)* [16]. One of the reasons for this recommendation is the known characteristic of hypercortisolism (particularly if severe) that the kidney enzyme 11b-hydroxysteroid dehydrogenase type 2 cannot convert all cortisol to cortisone. As a result, an excessive amount of cortisol binds to the mineralocorticoid receptor and produces the effects of mineralocorticoid surplus, including salt and water accumulation with BP increase and K^+ decrease [13]. Therefore spironolactone or e.g. eplerenone can be recommended for patients with CS/CD. MRA spironolactone is expected to be advantageous [14] due to excessive action of both glucocorticoids and mineralocorticoids "non-selective" CCBs are also candidates for CS/CD patients [16] because they are an essential part of the most triple antihypertensive therapies [9].

The additional reason to consider *CCBs* in CS/CD patients is that short-term variability of BP is higher in CS patients [17] and it is known that CCBs and ACE inhibitors diminish visit-to-visit BP variations [18] particularly if they are obese and their HTN is severe. The escalation of antihypertensive treatment is to be expected, because HTN was controlled in only 15% of CS patients [19].

In addition to its own significance *dyslipidemia* is an important problem in CS/CD patients because it is prevalent and clustered with other risk factors of atherosclerosis [5]. Moreover, this association between risk factors is quantitative, e.g., LDL-cholesterol is significantly and independently associated with systolic BP in CS/CD [38]. A common pattern of dyslipidemia in CS/CD is represented by the increase in LDL-cholesterol and triglycerides and decrease of HDL-cholesterol [39].

Chronic hypercortisolemia leads to insulin resistance; therefore CS/CD is the metabolic syndrome's archetype. Overweight or obesity is found in > 50% of CS/CD patients and DM is also very prevalent (up to 50%) [40]. The obesity and DM, prevalent characteristics of CS/CD patients, make hyperlipidemia more difficult to control [41]. It is particularly so if hypercortisolism is not controlled. Even following the effective therapy of CD (despite a decrease of BP and body mass index) the majority

Table 1 Some cardiologic drugs and diagnostic procedures we suggest for more regular use in CS/CD patients

Comorbidity /Characteristic of CS/CD	Reference confirming that this comorbidity /characteristic is prevalent in CS/CD	Drug (or diagnostic procedure) suggested for PRIMARY prevention /EARLY treatment (or early diagnosis)	Reference confirming the rationale for the cited drug (or diagnostic procedure) for particular co-morbidity /characteristic
HTN (early treatment)	[5,6]	RAAS blocker, spironolactone, consider timely (using ABPM) CCB, diuretic and BB	[15,16]
Hyperlipidemia (early treatment)	[5]	depending upon FHS or SCORE, consider statin	[20-22]
HF (primary prevention)	[5,23]	RAAS blocker, spironolactone	[24,25]
CAD (early diagnosis)	[5,26,27]	Pretest probability of CAD, ECG, exercise test, CT calcium score	[28,29]
CAD (primary prevention)	[5,26,30]	Consider aspirin and statin	[29,31]
Hypokalemia (early treatment)	[32]	spironolactone, RAAS blocker	[33,34]
VTE (early diagnosis)	[35]	Clinical prediction rule, D dimer, venous ultrasound	[36,37]

Legend: CS/CD – Cushing's syndrome/Cushing's disease; HTN – arterial hypertension; RAAS – renin-angiotensin-aldosterone system; ABPM – ambulatory blood pressure monitoring; CCB - calcium channel blocker; BB – beta-blocker; FHS – Framingham Risk Score; SCORE – Systematic COronary Risk Evaluation; HF – heart failure; CAD – coronary artery disease; CT – computerized tomography; ECG – electrocardiogram.

of patients (56%-76%) one year later still had obesity, HTN, DM, high cholesterol, and triglyceride levels [40].

In line with this, obesity (especially visceral) often continues even after surgical remission in CS/CD patients [41]; it may contribute to the persistence of hypercholesterolemia and hypertriglyceridemia [39]. This persistence of dyslipidemia can result from the continuation of increased BMI [41].

Unfortunately, some drugs used to suppress adrenal glands in CS/CD have unwanted effects in worsening dyslipidemia [41,42], which questions their clinical benefit. The significance of dyslipidemia and its association with other risk factors of atherosclerosis leads to the suggestion for its aggressive therapy [42]. Therefore a scene is set for treating hyperlipidemia in CS/CD. On an individual basis, eligibility for treatment can be estimated using the patient's Framingham Risk Score (FHS) or Systematic COronary Risk Evaluation (SCORE) [20-22] to evaluate the risk of CAD and mortality (and the need for antihyperlipidemic therapy). As in most other patients, for these with CS/CD in the first place, a statin ought to be considered.

The caution is advised because of *steroid myopathy* which is often present in CS/CD [43]. Proximal myopathy is regarded as additionally suggestive of CS (similarly to purple striae) [43,44]. It is a toxic non-inflammatory myopathy that dominantly affects pelvic muscles with consequent difficulties to stand up and climb up [45]. Steroid myopathy is the most prevalent among drug-induced myopathies; its incidence is around half of corticosteroid-using patients for prolonged periods [45]. The diagnostic approach is not standardized, and it is not easy to quantify the changes and to follow-up such patients adequately [43]. In addition to muscle symptoms (i.e. myalgia), weakness of proximal muscles can complicate statin use [45,46]. Unfortunately, muscle strength testing is not frequently performed; reports demonstrated muscle weakness in >10% of statin users [46]. Therefore, the likelihood of an indication for statin is substantial in CS/CD patients, but the follow-up ought to be adequate, particularly as far as steroid myopathy and hepatic lesions are concerned.

The risk of *HF* is increased in CS/CD patients, up to 6-fold [32]. The most important risk factors of HF are clustered in CS/CD, such as HTN, CAD, obesity, and DM [5]. Moreover, a direct effect of glucocorticoid excess upon cardiomyocytes is probable [23,47-49]. *An echocardiogram* is needed in CS/CD patients to evaluate the presence of structural and functional abnormalities of the heart, which are common in CS/CD patients, starting from left ventricular hypertrophy (LVH) as a result of several aforementioned risk factors. The echocardiogram is obviously indicated, and it is hopefully done in most CS/CD patients.

RAAS blocker and potassium sparring diuretic (spironolactone in the first place) can be recommended for *HF* primary prevention in CS/CD patients with HTN. In CS/CD patients with HTN and "borderline" HF (incipient symptoms with minimal NT pro-BNP elevation): in the first line diuretic *(MRA), RAAS blocker, and certain BBs (bisoprolol, carvedilol, metoprolol succinate [50] and nebivolol [25])* can be recommended. An adequate choice of certain BBs is needed because they are a very different class of drugs [51]. Also SGLT2 inhibitors can be suggested for evaluation in CS/CD patients.

Cardiovascular diseases are the main cause of death in CS/CD patients [52]. Therefore, it is reasonable to look for *CAD* in many CS/CD patients. Their age, symptoms, and risk factors can help us estimate the risk [28]. It is documented that CAD risk in many CS/CD patients is high or very high [26]. Moreover, CAD is more prevalent in CS/CD vs. controls (general population) up to 17 times [27].

In addition to the estimation of CAD probability for early diagnosis, several methods are widely available including ECG, exercise test, coronary artery calcium score, etc. Moreover, Holter is needed for arrhythmia and ischemia detection, as the risk of atrial fibrillation is also increased in CS/CD [32]. Indeed, for the estimation of AF risk, various risk scores can be useful [53]. In CS/CD at high risk of CAD we ought to consider ASA [29] and statin [20-22] in the primary prevention. In CS/CD patients with HTN at high risk of CAD, there is a rationale to consider RAAS blocker, and CCB or BB [9].

For *early detection of VTE*, one should recognize elevated risk in CS/CD patients. It is reasonable to use clinical prediction rules, D dimer, and venous ultrasound more liberally and more frequently in patients with CS/CD vs. without it.

To sum up, it is important that the clustering of cardiovascular risk factors in CD and CS due to ongoing long-term administration of high-dose glucocorticoid treatment is estimated by FRS and SCORE as high or very high [5]. Therefore, the cardiologic approach is typical for patients at high risk of CAD, with additional attention on more regular use of holter and ABPM.

Conclusion

The risk of cardiovascular events is high enough or will be high enough in the majority of CS/CD patients to warrant a cardiologic work-up. Due to scarce data on the individual benefit of examinations and tests more studies are needed to explore the cost-effectiveness of several cardiologic diagnostic and therapeutic procedures.

To our opinion, the vast majority of CS/CD patients ought to be evaluated as candidates for Holter and 24h ABPM in addition to echocardiography, due to the increased risk of numerous cardiovascular diseases. Aspirin, RAAS blocker, MRA, and statin may be subjects of the individual evaluation for the primary cardiologic prevention of CAD and HF in CS/CD patients.

References

1. Fleseriu M. Salivary Cortisol in the Diagnosis of Cushing Syndrome, Always More Than One! J Endocr Soc 2020; 4(10):bvaa109. doi: 10.1210/jendso/bvaa109.
2. Chaudhry HS, Singh G. Cushing Syndrome. Treasure Island (FL): StatPearls Publishing, 2020. PMID: 29261900
3. Nguyen HCT, Anastasopoulou C. Iatrogenic Cushing Syndrome. Downloaded from: https://emedicine.medscape.com/article/117365-overview (1/11/2021).
4. Suarez MG, Stack M, Hinojosa-Amaya JM, et al. Hypercoagulability in Cushing Syndrome, Prevalence of Thrombotic Events: A Large, Single-Center, Retrospective Study. J Endocr Soc 2019; 4(2):bvz033. doi: 10.1210/jendso/bvz033. PMID: 32064411;
5. Koracevic G, Stojkovic M, Lovic D, et al. Should Cushing's Syndrome be Considered as a Disease with High Cardiovascular Risk in Relevant Guidelines? Curr Vasc Pharmacol 2020; 18(1):12-24. doi: 10.2174/1570161116666181005122339.
6. Ragnarsson O, Olsson DS, Papakokkinou E, et al. Overall and Disease-Specific Mortality in Patients With Cushing Disease: A Swedish Nationwide Study. J Clin Endocrinol Metab 2019; 104(6):2375-2384. doi: 10.1210/jc.2018-02524. PMID: 30715394.
7. De Leo M, Pivonello R, Auriemma RS, et al. Cardiovascular disease in Cushing's syndrome: heart versus vasculature. Neuroendocrinology 2010; 92 Suppl 1:50-54. doi: 10.1159/000318566.
8. Peppa M, Krania M, Raptis SA. Hypertension and other morbidities with Cushing's syndrome associated with corticosteroids: a review. Integr Blood Press Control 2011; 4:7-16. doi: 10.2147/IBPC.S9486.
9. Williams B, Mancia G, Spiering W, et al. ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018; 39(33):3021-3104. doi: 10.1093/eurheartj/ehy339.
10. Umemura S, Arima H, Arima S, et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019). Hypertens Res 2019; 42(9):1235-1481. doi: 10.1038/s41440-019-0284-9.
11. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension 2020; 75(6):1334-1357. doi:10.1161/HYPERTENSIONAHA.120.15026
12. Koracevic G, Stojanovic M, Stojanovic S, Lovic D, Djordjevic M. Rationale to search for masked hypertension in severe Cushing's disease. Minerva Med (accepted for publication)
13. Ferriere A, Tabarin A. Cushing's syndrome: Treatment and new therapeutic approaches. Best Pract Res Clin Endocrinol Metab 2020; 34(2):101381. doi: 10.1016/j.beem.2020.101381.
14. Magiakou MA, Smyrnaki P, Chrousos GP. Hypertension in Cushing's syndrome. Best Pract Res Clin Endocrinol Metab 2006; 20(3):467-482. doi: 10.1016/j.beem.2006.07.006.
15. Cicala MV, Mantero F. Hypertension in Cushing's syndrome: from pathogenesis to treatment. Neuroendocrinology 2010; 92 Suppl 1:44-49. doi: 10.1159/000314315.
16. Barbot M, Ceccato F, Scaroni C. The Pathophysiology and Treatment of Hypertension in Patients With Cushing's Syndrome. Front Endocrinol (Lausanne) 2019;10:321. doi: 10.3389/fendo.2019.00321.
17. Rebellato A, Grillo A, Dassie F, et al. Ambulatory blood pressure monitoring-derived short-term blood pressure variability is increased in Cushing's syndrome. Endocrine 2014; 47(2):557-563. doi: 10.1007/s12020-014-0164-7.
18. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013; 34(28):2159-2219. doi: 10.1093/eurheartj/eht151.
19. Fallo F, Sonino N. Should we evaluate for cardiovascular disease in patients with Cushing's syndrome? Clin Endocrinol (Oxf) 2009; 71(6):768-771. doi: 10.1111/j.1365-2265.2009.03610.x.
20. Ko DT, Sivaswamy A, Sud M, et al. Calibration and discrimination of the Framingham Risk Score and the Pooled Cohort Equations CMAJ 2020; 192(17):E442-E449. doi: 10.1503/cmaj.190848.
21. Al-Shamsi S. Performance of the Framingham coronary heart disease risk score for predicting 10-year cardiac risk in adult United Arab Emirates nationals without diabetes: a retrospective cohort study. BMC Fam Pract 2020; 21(1):175. doi: 10.1186/s12875-020-01246-2.
22. Bruckert E, Parhofer KG, Gonzalez-Juanatey JR, et al. Proportion of High-Risk/Very High-Risk Patients in Europe with Low-Density Lipoprotein Cholesterol at Target According to European Guidelines: A Systematic Review. Adv Ther 2020; 37(5):1724-1736. doi: 10.1007/s12325-020-01285-2.
23. Sheikh T, Shuja H, Zaidi SR, Haque A. Glucocorticoid-induced cardiomyopathy: unexpected conclusion. BMJ Case Rep 2020; 13(11):e237173. doi: 10.1136/bcr-2020-237173.
24. Seferovic PM, Ponikowski P, Anker SD, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2019; 21(10):1169-1186. doi: 10.1002/ejhf.1531.
25. Yancy CW, Jessup M, Bozkurt B,et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017; 136(6):e137-e161. doi: 10.1161/CIR.0000000000000509.
26. Arnaldi G, Mancini T, Polenta B, Boscaro M. Cardiovascular risk in Cushing's syndrome. Pituitary 2004; 7(4):253-256.
27. Ahn CH, Kim JH, Park MY, Kim SW. Epidemiology and Comorbidity of Adrenal Cushing's Syndrome: A Nationwide Cohort Study. J Clin Endocrinol Metab 2020:dgaa752. doi: 10.1210/clinem/dgaa752.
28. Reeh J, Therming CB, Heitmann M, et al. Prediction of obstructive coronary artery disease and prognosis in patients with suspected stable angina. Eur Heart J 2019;40(18):1426-1435. doi: 10.1093/eurheartj/ehy806.
29. Cainzos-Achirica M, Miedema MD, McEvoy JW, et al. Coronary Artery Calcium for Personalized Allocation of Aspirin in Primary Prevention of Cardiovascular Disease in 2019: The MESA Study (Multi-Ethnic Study of Atherosclerosis). Circulation 2020; 141(19):1541-1553. doi: 10.1161/CIRCULATIONAHA.119.045010. PMID: 32233663;
30. Park MY, Kim SW. Epidemiology and Comorbidity of Adrenal Cushing's Syndrome: A Nationwide Cohort Study. J Clin Endocrinol Metab 2020:dgaa752. doi: 10.1210/clinem/dgaa752.
31. Stewart J, Addy K, Campbell S, Wilkinson P. Primary prevention of cardiovascular disease: Updated review of contemporary guidance and literature. JRSM Cardiovasc Dis 2020;9:2048004020949326. doi: 10.1177/2048004020949326.
32. Koracevic G, Mićić S, Stojanović M, et al. High likelihood for atrial fibrillation in Cushing's syndrome. Eur Rev Med Pharmacol Sci 2020; 24(3):1391-1397. doi: 10.26355/eurrev_202002_20196.
33. Langote A, Hiremath S, Ruzicka M, McCormick BB. Spironolactone is effective in treating hypokalemia among peritoneal dialysis patients. PLoS One 2017; 12(11):e0187269. doi: 10.1371/journal.pone.0187269.
34. Gilligan S, Raphael KL. Hyperkalemia and Hypokalemia in CKD: Prevalence, Risk Factors, and Clinical Outcomes. Adv Chronic Kidney Dis 2017; 24(5):315-318. doi: 10.1053/j.ackd.2017.06.004.
35. Koraćević G, Stojanović M, Petrović S, et al. Cushing's syndrome, a risk factor for venous thromboembolism is a candidate for guidelines. Acta Endocrinol (Buchar) 2020; 16(2):123-128. doi: 10.4183/aeb.2020.123. PMID: 33029226
36. Konstantinides SV, Meyer G, Becattini C, et al.The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). 2019 ESC

Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J 2019; 54(3):1901647. doi: 10.1183/13993003.01647-2019.

37. Streiff MB, Agnelli G, Connors JM, et al. Guidance for the treatment of deep vein thrombosis and pulmonary embolism. J Thromb Thrombolysis 2016; 41(1):32-67. doi: 10.1007/s11239-015-1317-0
38. Qin L, Zhu X, Liu X,et al. Evaluation of lipid profile and its relationship with blood pressure in patients with Cushing's disease. Endocr Connect. 2018; 7(5):637-644. doi: 10.1530/EC-18-0010.
39. Barbot M, Zilio M, Scaroni C. Cushing's syndrome: Overview of clinical presentation, diagnostic tools and complications. Best Pract Res Clin Endocrinol Metab 2020; 34(2):101380. doi: 10.1016/j.beem.2020. PMID: 32165101
40. Pivonello R, De Martino MC, De Leo M, Simeoli C, Colao A. Cushing's disease: the burden of illness. Endocrine 2017; 56(1):10-18. doi: 10.1007/s12020-016-0984-8.
41. Feingold KR, Brinton EA, Grunfeld C. The Effect of Endocrine Disorders on Lipids and Lipoproteins. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc, 2000
42. Pivonello R, De Leo M, Cozzolino A, Colao A. The Treatment of Cushing's Disease. Endocr Rev 2015; 36(4):385-486. doi: 10.1210/er.2013-1048.
43. Minetto MA, Caresio C, Salvi M, et al. Ultrasound-based detection of glucocorticoid-induced impairments of muscle mass and structure in Cushing's disease. J Endocrinol Invest 2019; 42(7):757-768. doi: 10.1007/s40618-018-0979-9.
44. Pérez EG, Hernández EA, Zuñiga AE, et al. Comparación del índice de gravedad del síndrome de Cushing entre pacientes con origen endógeno y yatrogénico de la enfermedad [Comparison of the severity index in Cushing's syndrome between patients with endogenous and iatrogenic disease]. Endocrinol Nutr 2010; 57(9):426-433. doi: 10.1016/j.endonu.2010.06.011.
45. Surmachevska N, Tiwari V. Corticosteroid Induced Myopathy. Treasure Island (FL): StatPearls Publishing, 2020.
46. Dobkin BH. The insidious impact of under-diagnosed proximal weakness induced by statins. Expert Rev Neurother 2020:1-9. doi: 10.1080/14737175.2021.1866988.
47. Hey TM, Dahl JS, Brix TH, Søndergaard EV. Biventricular hypertrophy and heart failure as initial presentation of Cushing's disease. BMJ Case Rep 2013; 2013:bcr2013201307. doi: 10.1136/bcr-2013-201307.
48. Aydoğan Bİ, Gerede DM, Canpolat AG, Erdoğan MF. Cushing's Disease Presented by Reversible Dilated Cardiomyopathy. Case Rep Cardiol 2015; 2015:980897. doi: 10.1155/2015/980897.
49. Marchand L, Segrestin B, Lapoirie M, et al. Dilated Cardiomyopathy Revealing Cushing Disease: A Case Report and Literature Review. Medicine (Baltimore) 2015; 94(46):e2011. doi: 10.1097/MD.0000000000002011.
50. Ponikowski P, Voors AA, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure Web Addenda 2016 Addenda Web Tables. Eur Heart J 2016 https://www.escardio.org/static_file/Escardio/Guidelines/ehw128_Addenda.pdf [March 21st, 2020.]
51. Koracevic G, Micic S, Stojanovic M, et al. Compelling Indications Should be Listed for Individual Beta-Blockers (Due to Diversity), Not for the Whole Class. Curr Vasc Pharmacology 2021, doi: 10.2174/1570161118666200518113833 (accepted for publication)
52. Roldán-Sarmiento P, Lam-Chung CE, Hinojosa-Amaya JM, et al. Diabetes, Active Disease, and Afternoon Serum Cortisol Levels Predict Cushing's Disease Mortality: A Cohort Study. J Clin Endocrinol Metab 2021; 106(1):e103-e111. doi: 10.1210/clinem/dgaa774.
53. Orozco-Beltran D, Quesada JA, Bertomeu-Gonzalez V, et al. A new risk score to assess atrial fibrillation risk in hypertensive patients (ESCARVAL-RISK Project. Sci Rep 2020; 10(1):4796. doi: 10.1038/s41598-020-61437-w.