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INVITED REVIEW

Management of hypertension and coronary artery disease in vasculitis patients using glucocorticoids

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ABSTRACT

Systemic vasculitis is an autoimmune disorder characterized by inflammation and damage to blood vessels, often involving multiple organ systems. Glucocorticoids (GCs) are a cornerstone in managing vasculitis and other rheumatologic conditions due to their potent anti-inflammatory properties, but their use is associated with significant systemic side effects. This review evaluates the cardiovascular (CV) risks associated with glucocorticoid use, focusing on hypertension and atherosclerosis, and highlights strategies for minimizing these risks while managing systemic inflammation in vasculitis patients. Glucocorticoids, despite their efficacy in disease management, contribute to CV complications in a dose- and duration-dependent manner. Hypertension arises through mechanisms such as nitric oxide suppression, renin-angiotensin-aldosterone system activation, and vascular effects. Atherosclerosis is accelerated by endothelial dysfunction, oxidative stress, and inflammation, increasing risks for coronary artery disease and acute CV events. Daily doses exceeding 5 mg of prednisolone are linked to a marked rise in CV risks, even with short-term use. Moreover, systemic inflammation from vasculitis compounds these risks, making it challenging to disentangle GC side effects from the underlying disease pathology. Glucocorticoid therapy requires careful management, prioritizing the lowest effective dose and shortest duration possible. Routine CV risk assessments, blood pressure monitoring, and targeted interventions such as lifestyle modifications and pharmacologic therapies are crucial for mitigating adverse outcomes. Future studies should aim to define "safe" GC thresholds and refine treatment protocols to balance efficacy and safety in vasculitis management.

Keywords: atherosclerosis, cardiovascular risk, glucocorticoids, hypertension, systemic vasculitis, rheumatology.

Introduction

Systemic vasculitis is an autoimmune disorder that damages blood vessels of various sizes, affecting one or multiple organ systems [1]. These conditions can be categorized by vessel size and may arise as primary pathologies or secondary to connective tissue disorders or drug effects. Chronic inflammation from these disorders is also associated with myocardial ischemia and fibrosis and higher incidences of pericarditis and cardiomyopathies, which impair cardiac function and contribute to heart failure [2].

Glucocorticoids regulate physiological processes as critical modulators in energy metabolism, blood pressure (BP) regulation, mood, memory, and stress responses [3]. They are produced in the zona fasciculate of the adrenal cortex and released into the bloodstream. After their release, they trigger circadian and pulsatile effects throughout the body. Their secretion is regulated by adrenocorticotropic hormone (ACTH) through the hypothalamic-pituitary-adrenal (HPA) axis [4].

The physiological effects of endogenous glucocorticoids are well-documented. In 1929, Philip Hench and colleagues discovered their anti-inflammatory properties [5]. Since then, exogenous steroids have been utilized in both endocrine and non-endocrine conditions [6]. Although they are used diagnostically for conditions like Cushing's disease and adrenal insufficiency, their anti-inflammatory properties are also applied in treating non-endocrine disorders such as asthma, chronic obstructive pulmonary disease (COPD), and chronic inflammatory bowel disease [7]. Due to their potent anti-inflammatory and immunosuppressive properties, glucocorticoids have become a mainstay in treating many rheumatologic conditions, such as vasculitis and rheumatoid arthritis [8].

The use of exogenous glucocorticoids entered therapeutic protocols in the late 1940s. Their potent effects and inadequate alternatives in treating rheumatologic diseases have resulted in widespread use. Their impact on disease control during acute flare-ups of vasculitis cannot be underestimated [9]. New-generation agents, while promising, have yet to demonstrate the same efficacy as glucocorticoids during acute exacerbations. Because of their systemic side effects, American and European Rheumatology societies advise using glucocorticoids as first-line therapy or as a bridging treatment until the effects of disease-modifying antirheumatic drugs (DMARDs) or biological agents become evident [10]. If used, they should be given at the lowest effective dose until other therapies become effective. Subsequently, a tapering regimen is recommended to discontinue GC therapy [11]. Despite these recommendations, a study conducted between 2006 and 2019 discovered that glucocorticoids were part of the initial treatment for 37.7% of patients diagnosed with from 0.5% to 1.8%, with the frequency of use increasing notably with age [12]. Glucocorticoids remain among the top 10 most prescribed medications in the United Kingdom [13,14].

Although glucocorticoids offer significant therapeutic benefits, they carry many side effects affecting multiple organ systems. Chronic use can lead to conditions such as osteoporosis, dysglycemia, cerebrovascular events, and infections [15,16]. Glucocorticoids are also known to increase CVD risk, particularly by precipitating hypertension, hyperlipidemia, and diabetes mellitus [17].

In earlier periods, it was believed that non-systemic applications might limit side effects. However, research has demonstrated that glucocorticoids produce similar systemic side effects regardless of the route of administration [16,18]. Aside from intravenous use, side effects are most commonly observed with oral and intra-articular administration [19]. Given the current therapeutic landscape, it is unlikely that glucocorticoids will be completely phased out from treating vasculitis and other rheumatologic disorders. Therefore, clinicians must be aware of the potential side effects, especially CV morbidity and mortality, to ensure early detection and primary prevention.

The CV risks and benefits associated with glucocorticoid use remain controversial, and the question of whether there is a safe and effective dose or duration of glucocorticoid therapy is still debated. It is generally believed that the risk of CVD may be minimized with low doses and short durations of use. However, some research indicates that even a single dose or short-term treatment (66-72 hours) can have systemic side effects. For instance, the use of 20 mg for four days may induce hypertension [17].

Glucocorticoids have been associated with an increased risk of all-cause-of mortality. Most studies have indicated that a dose of 5 mg of prednisolone or its equivalents is considered a safe dose [20]. In a study involving glucocorticoid naïve RA patients, the risk of CV events associated with chronic glucocorticoid use was evaluated based on daily dose, cumulative dose, and treatment duration of six months to one year. After adjusting for traditional CVD risk factors and disease duration, it was shown that prednisolone use at a daily dose of less than 5 mg, a cumulative dose of less than 750 mg over six months, and less than 1100 mg over one year did not increase CVD risk [20]. However, doses exceeding 5 mg per day and short-term cumulative doses exceeding these thresholds were associated with an increased risk of CVD. The group that developed CV events tended to have higher mean ages, more traditional risk factors, higher disease activity, longer disease durations, and were less likely to use DMARDs. A meta-analysis found that RA patients have a 50% increased risk of CV events [21].

Glucocorticoids may increase the risk of CV events by promoting two critical CV risk factors: HT and atherosclerosis.

Hypertension

Glucocorticoid-induced hypertension gained attention due to its high prevalence (25-93%) as a comorbidity in Cushing's syndrome patients [22]. Following the recognition of hypertension in patients with endogenous steroid excess, the effects of exogenous steroid use on BP have been studied [23]. Both endogenous and exogenous excess glucocorticoids have been shown to cause hypertension. Studies have identified daily glucocorticoid dose and family history of essential hypertension as significant risk factors for glucocorticoid-induced hypertension.

Initially, it was thought that the hypertensive effects of glucocorticoids were primarily due to their mineralocorticoid activity [24]. While mineralocorticoid receptor activation plays a role in hypertension development, it is not the sole or even primary factor, as synthetic glucocorticoids exhibit minimal mineralocorticoid effects. Furthermore, research in human and animal models has shown that spironolactone cannot prevent glucocorticoid-induced hypertension [25]. Sodium reabsorption at the renal level is not an essential mechanism in glucocorticoid-induced hypertension either [26]. No significant increase in sympathetic activity has been observed. Over time, it has become clear that glucocorticoid-induced hypertension is a complex condition involving multiple systems.

Glucocorticoids contribute to hypertension by affecting nitric oxide (NO) release in the central nervous system, activating the renin-angiotensin-aldosterone system (RAAS), and promoting cardiac hypercontractility while increasing sodium reabsorption in the kidneys [23]. They also promote hypertension through mechanisms that potentiate their systemic effects on the liver and adipose tissue. Glucocorticoid receptors are known to be present in both vascular smooth muscle and endothelial cells [27]. Although glucocorticoids do not alter plasma arginine vasopressin levels, their impact on vascular smooth muscle increases angiotensin II V1a receptor expression and enhances sodium and calcium influx into cells [28]. In vitro studies have also shown that glucocorticoids reduce vascular reactivity and inhibit the synthesis of prostacyclin and nitric oxide, leading to vasoconstriction and, ultimately, hypertension.

In Addison's disease, the hypertensive response to glucocorticoid therapy occurs too rapidly to be explained by renal mechanisms alone, highlighting the role of the vascular bed in the acute regulation of BP [29]. This suggests that glucocorticoid-induced hypertension may develop via direct effects on vascular smooth muscle even during short-term use [30]. In general, acute glucocorticoid-induced hypertension is mediated through vascular mechanisms, while chronic hypertension develops through renal mechanisms. In addition, secondary hypertension resulting from glucocorticoid use tends to elevate systolic BP more than diastolic BP. After oral glucocorticoid administration, BP increases within 24 hours and peaks within the first few days [31]. Glucocorticoids disrupt circadian rhythms, resulting in inadequate nocturnal BP reduction [32]. This condition leads to non-dipping hypertension.

In the general population, an increase of 20 mmHg in systolic BP and 10 mmHg in diastolic BP doubles the risk of cardiovascular disease and ischemic heart disease mortality [33]. Vasculitis patients often receive glucocorticoid therapy for at least three months following disease flare-ups, with the cumulative dose increasing with prolonged use. In one study, hypertension developed in 9% of patients after three months of glucocorticoid therapy [34]. Among patients receiving high doses, the incidence of hypertension reached 30%, and among those over 65 years old, the rate was 37% [35] . Although daily doses under 7.5 mg are considered relatively safe, the risk of hypertension increases with both daily and cumulative doses [36]. A retrospective cohort study involving 71,642 patients confirmed that the incidence of hypertension rises with increasing cumulative glucocorticoid exposure. Patients were stratified into low, medium, and high cumulative dose groups, with hypertension incidence rates of 14%, 20%, and 30%, respectively [31].

In RA patients without a prior diagnosis of hypertension, glucocorticoid use was associated with a 17% increase in the risk of developing hypertension [36]. Additionally, 40% of patients who developed secondary hypertension from glucocorticoid use did not receive antihypertensive therapy, leaving them untreated for one of the most modifiable CVD risk factors. Furthermore,

30% of patients did not take BP measurements during follow-up visits within two years of initiating glucocorticoid therapy [36].

Regular BP monitoring should be performed during follow-up visits, and patients should be encouraged to monitor their BP. Most patients under GC treatment develop Grade-1 or Grade-2 hypertension. Before establishing a treatment protocol, scoring patients based on their CVD risk using their BP measurements and identifying their position on the risk scale is crucial [37]. The most critical step in treatment is to discontinue glucocorticoids or administer the lowest effective dose. Lifestyle changes, including dietary modifications, increased physical activity, smoking cessation, and weight loss, should be recommended to patients. Medical intervention, in addition to lifestyle modifications, is vital for preventing hypertensive organ damage and for the ongoing management of vasculitis. Medical treatment aims to reduce BP to below 130/80 mmHg [38]. From a pharmacological standpoint, due to the increased activation of the RAAS, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and nitric oxide (NO) donors such as L-arginine may be considered as first-line treatment options. Mineralocorticoid receptor antagonists (MRAs) and diuretics can be the next option. Contrary to their anticipated outcomes, calcium channel blockers (CCBs) and beta blockers are generally found to be ineffective in managing glucocorticoid-induced hypertension. Additionally, clinicians should consider using beta-blockers and thiazide diuretics, with careful attention to their potential adverse effects on glucose metabolism. It is also essential to monitor for hypokalemia, which can occur as a side effect of thiazide diuretics.

Atherosclerosis and Coronary Heart Disease

Atherosclerosis is a chronic, progressive inflammatory condition characterized by arterial narrowing, primarily due to vascular remodeling and the buildup of atherosclerotic plaques [39]. In patients with Cushing's syndrome, conditions indicating the presence of atherosclerosis, such as elevated levels of low-density lipoprotein (LDL), increased carotid intima-media thickness (IMT) and reduced carotid artery lumen diameter, are observed compared to individuals without the syndrome, independent of traditional cardiovascular risk factors such as smoking, body mass index (BMI), and hypertension [40]. Experimental studies using animal models further support these findings, demonstrating the pivotal role of glucocorticoids in the progression of atherosclerosis. In patients with prolonged glucocorticoid use (≥ five years), carotid plaques and peripheral artery disease are more prevalent compared to those with short-term use [41].

Glucocorticoids affect vascular function by modulating both vasoconstriction and vasodilation pathways. Elevated levels of endothelin-1 (ET-1), a potent vasoconstrictor, have been linked to atherosclerosis and contribute to increased vascular constriction [42]. Additionally, the overactivation of the RAAS, mainly through AngII, exacerbates vasoconstriction and endothelial injury. Regarding vasodilation, glucocorticoids inhibit the production of critical vasodilators such as nitric oxide (NO) and prostacyclin [43,44]. Chronic glucocorticoid use has been associated with increased production of reactive oxygen species (ROS), which decreases NO bioavailability and further damages the vascular endothelium. The other cause of endothelial dysfunction is impaired endothelial progenitor cell (EPC) regulation. In individuals using glucocorticoids, there is a reduction in circulating EPCs. Consequently, endothelial-related vasodilation decreases, and the mechanisms for endothelial repair become compromised. In damaged endothelium, the balance between thrombotic and antithrombotic factors is disrupted [44]. The balance between NO, thromboxane A2, and prostacyclin is altered, von Willebrand factor levels increase, fibrinolysis mechanisms decrease, and platelet aggregation is accelerated [45]. As a result, atherosclerosis is accelerated, and the risk of acute coronary events increases.

The ESC Prevention 2022 guidelines emphasize that patients with elevated systemic inflammation may face an increased risk of CV events [37]. Higher inflammatory burdens have been strongly associated with increased CV event risk, and C-reactive protein (CRP) is recognized as an essential indicator of this risk. However, most glucocorticoid studies have not adjusted their outcomes for disease activity or CRP levels. In rheumatologic diseases, key inflammatory molecules such as TNF-alpha and IL-6 play a significant role in

chronic inflammation and vascular damage [46]. Glucocorticoids suppress both these molecules, inhibiting the pro-inflammatory cascade. Nonetheless, glucocorticoids' metabolic effects may also contribute to CVD risk by promoting atherosclerosis.

In a cohort study involving 70,000 individuals, glucocorticoid doses exceeding 7.5 mg/day were associated with a 2- to 4-fold increase in adverse cardiovascular outcomes [47]. Notably, the risks of coronary heart disease (CHD) and heart failure (HF) were found to be greater than those of stroke (SVO). Due to their widespread use in treatment, ongoing research is into a "safe" daily dose of glucocorticoids. While some studies suggest that doses under 5 mg/day do not increase CVD mortality, others indicate that even with a daily dose of 5 mg, the CVD risk doubles. Furthermore, at 25 mg/day, the risk increases sixfold. This suggests that patients using glucocorticoids to manage inflammatory burden in rheumatic diseases remain in a high-risk category for CVD [17].

The cardiovascular risks associated with glucocorticoid use are comparable to those seen in patients with diabetes or diagnosed cardiovascular disease. Although glucocorticoid use in patients with inflammatory conditions is not explicitly included in CVD risk scoring, recent prevention guidelines for cardiovascular disease stress the importance of accounting for these factors.

Assessment of patients' risk profiles for coronary heart disease (CHD) is recommended. Although a constant multiplier has not been established for vasculitis patients, it is suggested that the risk determined by the SCORE-2 CVD risk calculator be multiplied by a factor of 1.5 for patients with RA [37]. This situation underlines the increased risk of CVD in systemic inflammatory processes. For secondary prevention, guidelines recommend administering low-dose colchicine (0.5 mg daily) to patients with uncontrolled risk factors despite other interventions. Additionally, research into IL-6 inhibitors and suppressing systemic inflammation in CHD patients is ongoing.

The necessity for coronary artery stenting should be thoroughly evaluated, as the metallic shafts of stents can provoke a foreign body reaction in already dysfunctional endothelium, potentially causing local plaque destabilization and accelerating atherosclerosis [48]. Many patients display ectatic coronary arteries due to chronic inflammation, which are more prone to frailty and have a higher risk of complications [49]. Antithrombotic therapy should be optimized, and the dosage of statin treatment should be adjusted to achieve the targets recommended by guidelines.

Take Home Messages

- Glucocorticoid use is associated with hypertension and atherosclerosis, with these effects being dose- and duration-dependent.
- When disease activity is high, systemic inflammation increases, leading to higher doses of glucocorticoids. Consequently, it is difficult to determine whether systemic complications arise from the glucocorticoid dose or the intense inflammation. Moreover, a "safe" glucocorticoid dose may not apply uniformly to all side effects. It is crucial to use glucocorticoids for the shortest duration and at the lowest effective dose possible, especially when the disease is in remission.
- Due to the elevated CVD risk in vasculitis patients, lifestyle modifications alone are insufficient. Instead, they should be regarded as high-risk, and appropriate medical treatment should be administered when necessary.

Author contribution

Study conception and design: SA, EBK; draft manuscript preparation: SA, EBK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Clifford AH, Cohen Tervaert JW. Cardiovascular events and the role of accelerated atherosclerosis in systemic vasculitis. Atherosclerosis 2021;325:8-15. https://doi.org/10.1016/j.atherosclerosis.2021.03.032

[2] Silveira LH. Cardiovascular Manifestations of Systemic Vasculitides. Curr Rheumatol Rep 2020;22(10):72. https://doi.org/10.1007/s11926-020-00952-1

[3] Ramamoorthy S, Cidlowski JA. Corticosteroids: Mechanisms of Action in Health and Disease. Rheum Dis Clin North Am 2016;42(1):15-31. https://doi.org/10.1016/j.rdc.2015.08.002

[4] Burford NG, Webster NA, Cruz-Topete D. Hypothalamic-Pituitary-Adrenal Axis Modulation of Glucocorticoids in the Cardiovascular System. Int J Mol Sci 2017;18(10):2150. https://doi.org/10.3390/ijms18102150

[5] Hench PS, Kendall EC. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone; Compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. Proc Staff Meet Mayo Clin 1949;24(8):181-97.

[6] Yanase T, Tajima T, Katabami T, et al. Diagnosis and treatment of adrenal insufficiency including adrenal crisis: A Japan Endocrine Society clinical practice guideline [Opinion]. Endocr J 2016;63(9):765-84. https://doi.org/10.1507/endocrj.EJ16-0242

[7] Kaplan AG. Inhaled Corticosteroid Treatment in Chronic Obstructive Pulmonary Disease (COPD): Boon or Bane?. J Am Board Fam Med 2020;33(2):289-302. https://doi.org/10.3122/jabfm.2020.02.190227

[8] Buttgereit F. Views on glucocorticoid therapy in rheumatology: The age of convergence. Nat Rev Rheumatol 2020;16(4):239-46. https://doi.org/10.1038/s41584-020-0370-z

[9] Kermani TA, Warrington KJ, Dua AB. Treatment Guidelines in Vasculitis. Rheum Dis Clin North Am 2022;48(3):705-24. https://doi.org/10.1016/j.rdc.2022.03.006

[10] Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76(6):960-77. https://doi.org/10.1136/annrheumdis-2016-210715

[11] Nagy G, Roodenrijs NM, Welsing PM, et al. EULAR definition of difficult-to-treat rheumatoid arthritis. Ann Rheum Dis 2021;80(1):31-5. https://doi.org/10.1136/annrheumdis-2020-217344

[12] van Staa TP, Leufkens HG, Abenhaim L, Begaud B, Zhang B, Cooper C. Use of oral corticosteroids in the United Kingdom. QJM 2000;93(2):105-11. https://doi.org/10.1093/qjmed/93.2.105

[13] Bénard-Laribière A, Pariente A, Pambrun E, Bégaud B, Fardet L, Noize P. Prevalence and prescription patterns of oral glucocorticoids in adults: A retrospective cross-sectional and cohort analysis in France. BMJ Open 2017;7(7):e015905. https://doi.org/10.1136/bmjopen-2017-015905

[14] NHS Business Service Authority. (2021). Prescription cost analysis-England 2020/21.

[15] Box CD, Cronin O, Hauser B. The Impact of High Dose Glucocorticoids on Bone Health and Fracture Risk in Systemic Vasculitides. Front Endocrinol (Lausanne) 2022;13:806361. https://doi.org/10.3389/fendo.2022.806361

[16] Phan K, Smith SD. Topical corticosteroids and risk of diabetes mellitus: Systematic review and meta-analysis. J Dermatolog Treat 2021;32(3):345-9. https://doi.org/10.1080/09546634.2019.1657224

[17] Pofi R, Caratti G, Ray DW, Tomlinson JW. Treating the Side Effects of Exogenous Glucocorticoids; Can We Separate the Good From the Bad?. Endocr Rev 2023;44(6):975-1011. https://doi.org/10.1210/endrev/bnad016

[18] Heffler E, Madeira LNG, Ferrando M, et al. Inhaled Corticosteroids Safety and Adverse Effects in Patients with Asthma. J Allergy Clin Immunol Pract 2018;6(3):776-81. https://doi.org/10.1016/j.jaip.2018.01.025

[19] Habib GS. Systemic effects of intra-articular corticosteroids. Clin Rheumatol 2009;28(7):749-56. https://doi.org/10.1007/s10067-009-1135-x

[20] Ocon AJ, Reed G, Pappas DA, Curtis JR, Kremer JM. Short-term dose and duration-dependent glucocorticoid risk for cardiovascular events in glucocorticoid-naive patients with rheumatoid arthritis. Ann Rheum Dis 2021;80(12):1522-9. https://doi.org/10.1136/annrheumdis-2021-220577

[21] Hannawi SM, Hannawi H, Al Salmi I. Cardiovascular Risk in Rheumatoid Arthritis: Literature Review. Oman Med J 2021;36(3):e262. https://doi.org/10.5001/omj.2021.25

[22] Pivonello R, Isidori AM, De Martino MC, Newell-Price J, Biller BMK, Colao A. Complications of Cushing's syndrome: State of the art. Lancet Diabetes Endocrinol 2016;4(7):611-29. https://doi.org/10.1016/S2213-8587(16)00086-3

[23] Goodwin JE, Geller DS. Glucocorticoid-induced hypertension. Pediatr Nephrol 2012;27(7):1059-66. https://doi.org/10.1007/s00467-011-1928-4

[24] Whitworth JA, Mangos GJ, Kelly JJ. Cushing, cortisol, and cardiovascular disease. Hypertension 2000;36(5):912-6. https://doi.org/10.1161/01.hyp.36.5.912

[25] Mangos GJ, Whitworth JA, Williamson PM, Kelly JJ. Glucocorticoids and the kidney. Nephrology (Carlton) 2003;8(6):267-73. https://doi.org/10.1111/j.1440-1797.2003.00215.x

[26] Li M, Wen C, Fraser T, Whitworth JA. Adrenocorticotrophin-induced hypertension: Effects of mineralocorticoid and glucocorticoid receptor antagonism. J Hypertens 1999;17(3):419-26. https://doi.org/10.1097/00004872-199917030-00016

[27] Provencher PH, Saltis J, Funder JW. Glucocorticoids but not mineralocorticoids modulate endothelin-1 and angiotensin II binding in SHR vascular smooth muscle cells. J Steroid Biochem Mol Biol 1995;52(3):219-25. https://doi.org/10.1016/0960-0760(94)00168-I

[28] Kornel L, Nelson WA, Manisundaram B, Chigurupati R, Hayashi T. Mechanism of the effects of glucocorticoids and mineralocorticoids on vascular smooth muscle contractility. Steroids 1993;58(12):580-7. https://doi.org/10.1016/0039-128x(93)90099-9

[29] Johannsson G, Falorni A, Skrtic S, et al. Adrenal insufficiency: Review of clinical outcomes with current glucocorticoid replacement therapy. Clin Endocrinol (Oxf) 2015;82(1):2-11. https://doi.org/10.1111/cen.12603

[30] Brotman DJ, Girod JP, Garcia MJ, et al. Effects of short-term glucocorticoids on cardiovascular biomarkers. J Clin Endocrinol Metab 2005;90(6):3202-8. https://doi.org/10.1210/jc.2004-2379

[31] Mebrahtu TF, Morgan AW, West RM, Stewart PM, Pujades-Rodriguez M. Oral glucocorticoids and incidence of hypertension in people with chronic inflammatory diseases: A population-based cohort study. CMAJ 2020;192(12):E295-301. https://doi.org/10.1503/cmaj.191012

[32] Ivy JR, Oosthuyzen W, Peltz TS, et al. Glucocorticoids Induce Nondipping Blood Pressure by Activating the Thiazide-Sensitive Cotransporter. Hypertension 2016;67(5):1029-37. https://doi.org/10.1161/HYPERTENSIONAHA.115.06977

[33] Baid S, Nieman LK. Glucocorticoid excess and hypertension. Curr Hypertens Rep 2004;6(6):493-9. https://doi.org/10.1007/s11906-004-0046-0

[34] Fardet L, Flahault A, Kettaneh A, et al. Corticosteroid-induced clinical adverse events: Frequency, risk factors and patient's opinion. Br J Dermatol 2007;157(1):142-8. https://doi.org/10.1111/j.1365-2133.2007.07950.x

[35] Sato A, Funder JW, Okubo M, Kubota E, Saruta T. Glucocorticoid-induced hypertension in the elderly. Relation to serum calcium and family history of essential hypertension. Am J Hypertens 1995;8(8):823-8. https://doi.org/10.1016/0895-7061(95)00149-J

[36] Costello RE, Yimer BB, Roads P, Jani M, Dixon WG. Glucocorticoid use is associated with an increased risk of hypertension. Rheumatology (Oxford) 2021;60(1):132-9. https://doi.org/10.1093/rheumatology/keaa209

[37] Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42(34):3227-337. https://doi.org/10.1093/eurheartj/ehab484

[38] Mancia G, Kreutz R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens 2023;41(12):1874-2071. https://doi.org/10.1097/HJH.0000000000003480

[39] Libby P. The changing landscape of atherosclerosis. Nature 2021;592(7855):524-33. https://doi.org/10.1038/s41586-021-03392-8

[40] Barahona MJ, Resmini E, Viladés D, et al. Coronary artery disease detected by multislice computed tomography in patients after long-term cure of Cushing's syndrome. J Clin Endocrinol Metab 2013;98(3):1093-9. https://doi.org/10.1210/jc.2012-3547

[41] Faggiano A, Pivonello R, Spiezia S, et al. Cardiovascular risk factors and common carotid artery caliber and stiffness in patients with Cushing's disease during active disease and 1 year after disease remission. J Clin Endocrinol Metab 2003;88(6):2527-33. https://doi.org/10.1210/jc.2002-021558

[42] Winkles JA, Alberts GF, Brogi E, Libby P. Endothelin-1 and endothelin receptor mRNA expression in normal and atherosclerotic human arteries. Biochem Biophys Res Commun 1993;191(3):1081-8. https://doi.org/10.1006/bbrc.1993.1327

[43] Iuchi T, Akaike M, Mitsui T, et al. Glucocorticoid excess induces superoxide production in vascular endothelial cells and elicits vascular endothelial dysfunction. Circ Res 2003;92(1):81-7. https://doi.org/10.1161/01.res.0000050588.35034.3c

[44] MacLeod C, Hadoke PWF, Nixon M. Glucocorticoids: Fuelling the Fire of Atherosclerosis or Therapeutic Extinguishers?. Int J Mol Sci 2021;22(14):7622. https://doi.org/10.3390/ijms22147622

[45] Rogers KM, Bonar CA, Estrella JL, Yang S. Inhibitory effect of glucocorticoid on coronary artery endothelial function. Am J Physiol Heart Circ Physiol 2002;283(5):H1922-8. https://doi.org/10.1152/ajpheart.00364.2002

[46] Yoshifuji H. Pathophysiology of large vessel vasculitis and utility of interleukin-6 inhibition therapy. Mod Rheumatol 2019;29(2):287-93. https://doi.org/10.1080/14397595.2018.1546358

[47] Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Ann Intern Med 2004;141(10):764-70. https://doi.org/10.7326/0003-4819-141-10-200411160-00007

[48] Khanna S, Garikapati K, Goh DSL, et al. Coronary artery vasculitis: A review of current literature. BMC Cardiovasc Disord 2021;21(1):7. https://doi.org/10.1186/s12872-020-01813-6

[49] Mavrogeni S, Manoussakis MN, Karagiorga TC, et al. Detection of coronary artery lesions and myocardial necrosis by magnetic resonance in systemic necrotizing vasculitides. Arthritis Rheum 2009;61(8):1121-9. https://doi.org/10.1002/art.24695