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ARTIGO DE REVISÃO

An integrative review of the methods used for cortisol assessment in clinical studies investigating the association between Blood Pressure and Cortisol Hormone

Hipertensão Arterial Sistêmica e o Hormônio Cortisol: uma revisão integrativa sobre as associações e os métodos de análises clínicas

Hipertensión Arterial Sistémica y la Hormona Cortisol: una revisión integrativa sobre las asociaciones y los métodos de análisis clínicos

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RESUMO

Justificativa e Objetivos: A Hipertensão Arterial Sistêmica (HAS) é uma condição de saúde que representa um problema de saúde pública mundial e sua relação com o hormônio cortisol ainda não está amplamente esclarecida. Dessa forma, esse estudo teve como objetivo identificar na literatura, as circunstâncias de existência de associação entre a HAS com o hormônio cortisol e os métodos clínicos utilizados para esta relação. **Métodos:** Realizou-se revisão Integrativa da Literatura, a partir de 17 artigos científicos publicados entre 2013 e 2017 identificados nas bases de dados EMBASE e PubMed, com os descritores hypertension e hydrocortisone, no idioma inglês. **Resultados:** Verificou-se associação da HAS com o aumento do cortisol na idade a partir de 62 anos, aumento de sódio na dieta, o hábito não ingerir o desjejum, aumento do consumo de cafeína, síndrome metabólica, obesidade, excesso de catecolaminas e alguns tipos de hormônios e biomarcadores. Os métodos clínicos mais utilizados para esta relação foram os testes de associação, feitos com a função renal e/ou cardíaca, síndrome metabólica, estresse, doenças crônicas associados com a avaliação de exames laboratoriais. **Conclusão:** Os resultados indicaram associação entre o cortisol e a Hipertensão no avançar da idade e estilo de vida, sendo os testes de associação os métodos mais utilizados.

Descritores: *Hipertensão. Cortisol. Hidrocortisona. Análises Clínicas. Cuidados de saúde.*

ABSTRACT

Background and Objectives: Systemic Arterial Hypertension (SAH) is a health condition that represents a global public health problem and its relation with the hormone cortisol is not yet widely understood. Thus, the present study aimed to identify in the literature the association among the SAH, the hormone cortisol and the clinical methods used to evaluate this relationship. **Methods:** An integrative literature review was carried out, based on 17 scientific articles published between 2013 and 2017 identified in the databases EMBASE and PubMed, with the descriptors hypertension and hydrocortisone in English language. **Results:** There was an association of SAH with

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increased cortisol at the age of 62 years, increased sodium in the diet, not eating breakfast, increased caffeine consumption, metabolic syndrome, obesity, excess catecholamine's, some types of hormones, and biomarkers. The most commonly used clinical methods for this relationship were association tests, performed with renal and / or cardiac function, metabolic syndrome, stress, chronic diseases associated with the evaluation of laboratory tests. **Conclusion:** The results indicated an association between cortisol and SAH with advancing age and lifestyle. Moreover, the association tests were the most used methods.
Keywords: *Hypertension. Cortisol. Hydrocortisone. Clinical analysis. Health care.*

RESUMEM

Justificación y objetivos: La Hipertensión Arterial Sistémica (HAS) es una afección de salud que representa un problema de salud pública mundial y su relación con la hormona cortisol aún no se conoce ampliamente. Por lo tanto, el presente estudio tuvo como objetivo identificar en la literatura la asociación entre la HAS, la hormona cortisol y los métodos clínicos utilizados para evaluar esta relación. **Métodos:** Se realizó una revisión integradora de la literatura, basada en 17 artículos científicos publicados entre 2013 y 2017 identificados en las bases de datos EMBASE y PubMed, con los descriptores hipertensión e hidrocortisona en idioma inglés. **Resultados:** Hubo una asociación de HAS con aumento de cortisol a la edad de 62 años, aumento de sodio en la dieta, falta de desayuno, aumento del consumo de cafeína, síndrome metabólico, obesidad, exceso de catecolaminas, algunos tipos de hormonas y biomarcadores. Los métodos clínicos más comúnmente utilizados para esta relación fueron las pruebas de asociación, realizadas con función renal y / o cardíaca, síndrome metabólico, estrés, enfermedades crónicas asociadas con la evaluación de pruebas de laboratorio. **Conclusión:** Los resultados indicaron una asociación entre el cortisol y la HAS con el avance de la edad y el estilo de vida. Además, las pruebas de asociación fueron los métodos más utilizados.
Palabras clave: *Hipertensão. Cortisol. Hidrocortisona. Analisis clinico. Cuidados de la salud.*

INTRODUCTION

Systemic Arterial Hypertension (SAH) is the major concern for the health public policies worldwide. SAH is highly prevalent, affecting approximately 10% to 25% of the general population. However, it remains underdiagnosed and poorly controlled, with high rates of morbidity and mortality being an important risk factor for heart and / or kidney diseases and stroke.[1-4]

The Renin-Angiotensin-Aldosterone System (RAAS) and the Hypothalamic-Hypophysis - Adrenal (HPA) axis, responsible for the regulation of blood pressure (BP), were reported to play an important role in the pathophysiology of SAH, and the glucocorticoid (cortisol) and mineralocorticoid (aldosterone) hormones are the respective effectors of these pathways.[5,6]

In fact, increased circulating or intracellular glucocorticoids levels are common and frequently associated with SAH. Cortisol is the main endogenous human glucocorticoid, secreted mainly in response to adrenocorticotropic hormone (ACTH), through the HPA axis. Additionally, cortisol is also known as the stress hormone, being influenced by a variety of biological or environmental factors.[7-11]

Acute or chronic increase in serum cortisol levels has been associated with increased BP, hyperglycemia, and endothelial dysfunction, which may be associated with cardiovascular risk. Cortisol is involved in the physiological regulation of BP by modulating the vasoconstrictor response via α 1 - adrenergic receptors through the action of catecholamine.[12-13]

Among the factors related to the prevalence of SAH in Brazilian adults, there are socio-demographic, behavioral, morbidities, biochemical and anthropometric alterations. One of the behavioral factors that is involved in the increase of the BP is the consumption of alcohol, which directly influences the heart, in the smooth muscles of the vessels, through the stimulation of the Sympathetic Nervous System (SNS) or RAAS, which can increase plasma levels of cortisol.[2,14]

Different methods have been used in clinical and scientific evaluations in different populations, and the most common is the anthropometric and hemodynamic tests. In view of the above and due to the particularities and limitations of each research methods, it is necessary to investigate the clinical methods used to evaluate the associations between cortisol and SAH, the relationship of which appears to be potentially harmful to health.[14,16]

In addition, it is expected that this study may contribute to increase the knowledge and orientation of new studies in this subject. Therefore, the objective of this study was to identify in the literature, through scientific evidence, the circumstances of existence of association between SAH and the hormone cortisol, and the clinical methods used for such evaluation.

METHODS

This Integrative literature review, which is considered as an instrument of the Evidence Based Practice (EBP), focus on clinical practice. Based on guiding question, data collection enables the elaboration of a summary of the results of all studies included in the analysis.[17,18]

The steps used in this integrative review were: 1) identification of the subject and selection of the hypothesis or question of the research; 2) determination of criteria for the databases search; 3) determination of inclusion and exclusion criteria of the studies; 3) definition of the information to be extracted from the studies; 4) data evaluation; 5) interpretation of results and 6) synthesis of knowledge.[17]

To address the study and the scope of the proposed

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goal, based on the PICO strategy, the following clinical question was formulated: *Which clinical methods are being used to verify the association between Blood Pressure and the Hormone cortisol?* P: population from clinical studies; I: cortisol assessment; C: no comparison factor, O: association between cortisol and BP levels.[19]

The included texts met the following criteria: complete articles, available free of charge in journals indexed in the EMBASE and PubMed databases, peer reviewed, with a description of clinical studies in humans, with mandatory evaluation of BP and biochemistry assessment of cortisol, published in the last five years (2013 to 2017). Selected articles were written in English. Articles that did not evaluate the direct association between cortisol and BP levels or those studies that were performed in patients with adrenal tumors or under corticoid treatment were excluded.

In the EMBASE database, the following descriptors were used: hypertension / AND 'hydrocortisone' AND 'human' AND (2013: py OR 2014: py OR 2015: py OR 2016: py OR 2017: py) AND 'article' / it AND ('clinical article' / of OR 'clinical protocol' / of OR 'controlled study' / of OR 'major clinical study' AND ([english] / lim OR), resulting in a previous selection of 212 articles. In the Pub Med database the following Medical Subject Heading (MeSH) terms were used for the searches: "Hypertension" [Mesh] AND "Hydrocortisone / analysis" [Mesh] AND ("2012/11/03" [PDA]: "2017/11/01 "[PDat] AND" humans "[MeSH Terms]), with a pre-selection of 49 articles.

The next step consisted of reading the title and the abstracts, and then the retained articles were submitted to full reading and detailed analysis. In the search and selection of articles, the strategy recommended by the PRISMA group was adopted as shown in the PRISMA Flowchart (Figure 1).[20]

For the step of full text analysis, a specific instrument was developed to extract and analyze data from the included studies. The tool comprised the following items: (1) publication, authors, journal and country; (2) objective of the study; (3) methods (study design, population, cortisol and BP assessment, other variables measured); and (4) Results. This stage was performed by four collaborators divided into two independent groups and reviewed by two reviewers, who reviewed and validated the data that were compiled. The results were compared and discussed, if necessary, until consensus.

RESULTS

The reviewed articles were published in scientific journals related to SAH and cardiovascular diseases (35.0%) and endocrinology (35.0%), as well as some multidisciplinary ones (30.0%). The number of publications was distributed over the years, 2013 (6.0%), 2014 (23.0%), 2015 (35.0%), 2016 (18.0%) and 2017 (18.0%). North America was the region with the largest number of articles (29.0%), followed by Europe (23.0%); Asia (24.0%); South America (12.0%) and Africa (12.0%).

The articles that were excluded (n = 244) from the study did not correspond to the proposed theme, since they were: referring to children, adolescents, obesity, stem cells, different types of diseases (Cushing's Syndrome, Ophthalmology, hearing aid, diabetes mellitus, tumors and occupational diseases), as well as different types of therapies, diets, drugs and surgeries.

After the full text reading, more four articles were excluded; three because they were related to patients with adrenal tumor and one that did not evaluate the association between cortisol and BP.

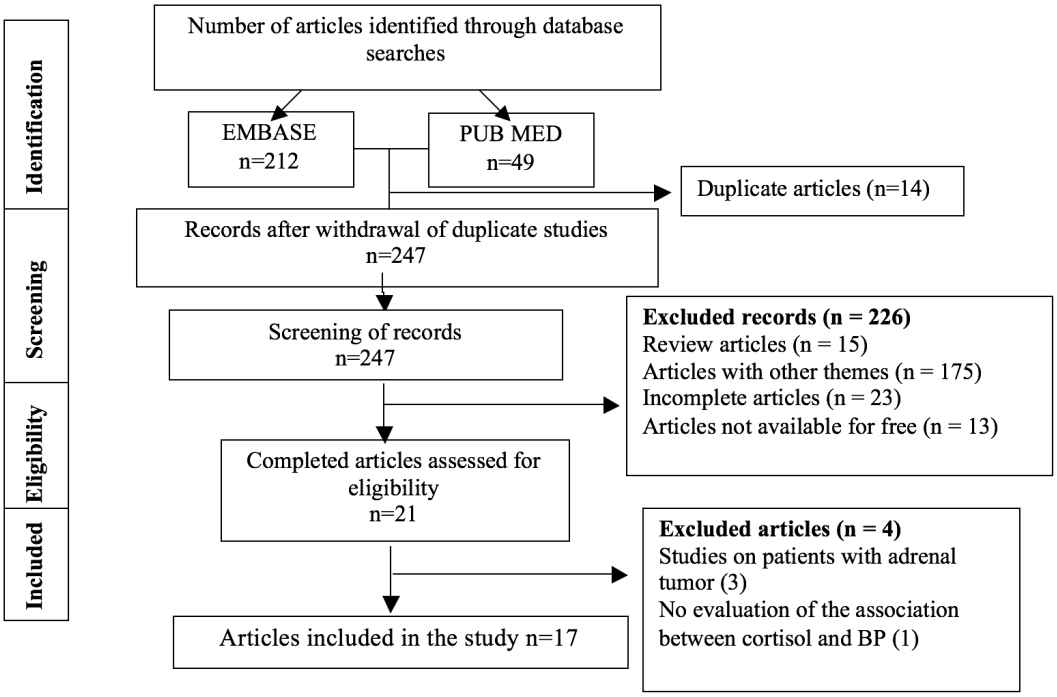

Figure 1. Flowchart of the selection of the studies, according to the PRISMA model.[20]

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Authors, country Journal and date	**Objective**	**Methods (study design, population, cortisol and BP assessment, other variables measured).**	**Results**
1. Ghazi et al. USA, 2017[21] American Journal of Hypertension	It is known that decreased renal 11-beta dehydrogenase type 2 (11β-HSD2) activities, reflected by an increased urinary free cortisol to cortisone ratio (UFF/UFE), is associated with having SAH (HTN). Objective were of determine if reduced 11β-HSD2 activity is also associated with having resistant HTN.	• Comparative clinical study. •Patients with Resistant SAH (RHTN) (n = 55) and with controlled SAH (n = 38). • Cortisol: 24 hour urine free for cortisone, (UFF/UFE). Method gas chromatography and mass spectrometry. •BP: auscultatory method. Other measures: All subjects underwent biochemical evaluation, including 24-hour UFF / UFE measurement.	The 24-hour UFF was 13.6 ± 11.8 Vs. 14.3 ± 10.7 µg / 24 h and the UFE was 64.9 ± 36.3 vs. 76.1 ± 44 µg / 24 h, so that the UFF / EFU was 0.22 ± 0.16 Vs. 0.19 ± 0.09 in RHTN versus the control group. This relationship was not associated with age, race, and gender and body mass index.
2. Malan et al.. South Africa, 2017[22] Hypertension Research	To evaluate the relationship between emotional distress, silent myocardial ischemia (SMI) and double product (systolic BP (SBP) x heart rate).	•Cross-sectional study. •Individuals of bi-ethnic cohorts from two South African sectors (n = 378). •Cortisol: Serum was collected before 09 h. (Method of assessment: ECLIA -Elecsys 2014, Roche Basel, Switzerland). •BP: double product of 24 h. Other measures: depressive symptoms, blood count, 24-hour electrocardiogram (ST depression).	The double product was positively associated with central obesity in all sexual groups and with cortisol in black men (P <0.05). Central obesity was related to cortisol.
3. Al-Abbasi et al., India, 2017[23] Biomedical Research	Triage of salivary and serum levels of cortisol and enzymatic activities of CK-BB, LDH and lipid profile in patients with stroke or diseases related to biomarkers for early non-invasive prevention of stroke.	•Comparative cross-sectional clinical study. •Adult male subjects (n = 8), divided into four groups: healthy normal, ischemic stroke, SAH and type II diabetes. •Cortisol: serum and saliva. Method not described. Analysis: kit BIOLINE (England). •BP: not described how it was measured. SAH was defined as BP ≥140 / 90 mm Hg. Other measures: serum glucose levels, total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c), enolase specific neuron activity, cortisol, lactate dehydrogenase (LDH) and creatine kinase (CK-BB) were measured in saliva and serum samples.	There was a significant increase in total serum and salivary cortisol (p <0.001) and LDL-c (p <0.01) in stroke and in hypertensive and diabetic patients compared to the control group.
4. Li et al., China, 2016[24] Kidney & Blood Pressure Research	To investigate the influence of environmental and inflammatory factors on metabolic diseases (obesity, type 2 diabetes, SAH and chronic kidney disease).	•Cross-sectional study. •Patients with essential SAH (n = 178). •Cortisol: serum. Method of analysis electrochemiluminescence. •BP: Essential SAH was defined as an average BP ≥140 / 90 mmHg on at least two different occasions without any evidence of secondary hypertension. Other measures: Fasting serum samples to plasma glucose levels, serum lipids, serum creatinine, glomerular filtration rate (eGFR) and anthropometric measures.	Serum cortisol levels were significantly higher in subjects whose eGFRcr-cys<90 ml/min/1.73 m2 than subjects whose eGFRcr-cys>90 ml/min/1.73 m2. Age, systolic blood pressure, and serum total cholesterol, uric acid, cortisol levels were significantly associated with eGFRcr-cys, serum levels of creatinine and cystatin C. However serum cortisol level was negatively correlated with eGFRcr-cys in subjects with essential SAH.
5. Daimon et al. Japan, 2016[6] J. Clin. Endocrinol. Metab.	To determine separately the effect of the HPA axis and the renin-angiotensin aldosterone system (RAAS) on SAH in a general population.	•Population study. •Japanese adults (n = 859) enrolled in the Iwaki study of 2014 and without SAH or steroid treatment. •Cortisol: serum, chemiluminescent enzyme immunoassay method. •BP: 30 minutes after arrival and after at least 10 minutes of rest, auscultatory method. Other measures: plasma aldosterone, ACTH, and plasma renin activity. Anthropometric data, fasting glucose, glycated hemoglobin (HbA1c), lipidic profile, uric acid (UA), urea nitrogen and creatinine.	The association of hypothalamus-pituitary-adrenal (HPA) axis and the renin-angiotensin aldosterone system (RAAS) were significantly to be associated with SAH prevalence and cortisol activity in a Japanese population.

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6. Pulopulos et al. Spain, 2016[25] Hormones and Behavior	To study the differences in cortisol on awakening (CAR) and in the global secretion of morning cortisol among hypertensive and normotensive elderly patients and to investigate the relationship between CAR and cognitive performance.	•Comparative cross-sectional clinical study. •Older adults (n = 58). •Cortisol: saliva, measured by immunoassay method. •BP: method of measurement not described. SAH was defined as SBP ≥ 140 mmHg, DBP mm 90 mmHg or on antihypertensive use. Other measures: cognitive performance.	Hypertensive participants had lower morning cortisol secretion. No differences were observed in CAR. A reduced-magnitude CAR was related to poorer cognitive / executive function in hypertensive and normotensive participants, but at a slower processing speed only in normotensive participants. Being treated with antihypertensive for a longer period of time was related to a CAR of greater magnitude and better performance in the executive function.
7. Byrd et al. USA, 2015[26] CardioRenal Medicine	To determine whether the serum cortisol--cortisone ratio (F / E ratio) is associated with BP in patients after significant weight loss (≥ 15% of baseline weight).	•Longitudinal intervention study for weight reduction. •Men with severe obesity, no diabetic (n=43), who participated in a weight control program. •Cortisol: serum by mass spectrometry. Subsequently established cortisol-cortisone ratio (F/E). • BP: method of measurement not described. Other measures: anthropometric data.	The basal F/E ratio tended to be associated with baseline diastolic blood pressure (DBP) and the change in serum F/E ratio correlated with change in DBP. The change in F/E ratio also tended to be associated with change in systolic BP.
8. Langerak et al. Netherlands, 2015[27] Clinical Endocrinology	To study the relationship between long-term cortisol levels and MetS in HIV-infected patients.	•Comparative cross-sectional clinical study. •HIV-infected patients (n = 126) and healthy controls (n = 191). •Cortisol: hair cortisol analyzed by the ELISA technique. •BP: method of measurement not described. Other measures: anthropometric data fasting glucose, insulin, lipid profile CD4 + cell count and HIV RNA.	The characteristic of MetS in the HIV group was elevated systolic BP (52.7%), followed by reduced HDL cholesterol (43.9%) and hypertriglyceridemia (42.9%). The of enlarged waist circumference (14.3%) yet elevated blood glucose levels (13.2%) was less frequent. There was a higher risk of MetS in patients with HIV with lower hair cortisol levels. Hair cortisol levels were not significantly different between patients with HIV and healthy controls.
9. Ceccato et al. Italy, 2015[28] Hormones	To evaluate if the rhythm of salivary cortisol production is affected by variables (such as age, gender, Metabolic Syndrome (MetS) and estrogen-progestogen therapy) in adults from the community.	•Cross-sectional study. •Adults (n = 120) from the community. •Cortisol: salivary, measured by immunoassay assay method; was collected 7 salivary samples: the first on awakening (F(0)) and 6 more (F(1.5), F(5), F(6), F(10), F(11.5) and F(14)) over the next 14 hours. Daily cortisol secretion was evaluated computing the Area Under the Curve (AUC (F0) (→) (F14)); the F (14) /F(0) ratio was calculated of cortisol rhythm. •BP: method of measurement not described. SAH was defined as SBP ≥130 mmHg, PAD 85 mmHg, or in use of medication. Other measures: anthropometric and metabolic data for MetS classification.	The association of study findings showed that the salivary cortisol daily cortisol secretion was evaluated computing the Area Under the Curve (AUC (F0) (→)(F14)); the F(14)/F(0) ratio was calculated as a marker of cortisol rhythm (AUC), is not influenced by age, gender, metabolic syndrome or use of estrogen-progestin therapy. But, only late-night salivary cortisol levels were found to increase with age and in patients with the MetS.
10. Witbracht et al. USA, 2015[29] Physiology & Behavior	To compare circulating cortisol levels as well as cardiovascular risk factors and the perceived stress among women who do not eat breakfast and those who routinely do this meal.	•Cross-sectional observational study. •Premenopausal women. •Cortisol: salivary, evaluated by immunoassay method. Not having breakfast (n = 30) or breakfast eater (n = 35). •BP: measured twice, with 1-minute interval, after 5 minutes of rest. Other measures: anthropometric and body composition data, stress questionnaires.	Associations indicate that not eating breakfast occurs increased concentrations of cortisol and much activity on the HPA axis, which if prolonged may increase the risk of SAH and cardio metabolic disease.
11. Ochiai et al. Japan, 2015[30] Int. J. Environ. Res. Public Health	To compare the physiological and psychological effects of a forest therapy program of relaxation and stress management in middle-aged men with activities of daily living on a normal day.	•Before and after clinical study. •Men between 40 and 73 years (n = 17). •Cortisol: serum. Method not described. •BP: isolated measure (before and after intervention). Other measures: urinary adrenaline, serum creatinine, questionnaires: semantic differential, mood state.	The associations revealed that forest therapy decreases systolic and diastolic blood pressure as well as levels of adrenaline in urine and serum cortisol.

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12. Hoefer et al. Austria, 2015[31] Journal of Vascular Surgery	Comparison of early sympathetic activity in carotid endarterectomy surgery among patients receiving regional anesthesia guided by ultrasound (US-RA) and patients undergoing general anesthesia (GA).	•Comparative cross-sectional clinical study. •Patients undergoing carotid endarterectomy randomized to receive US-RA (n = 32) or GA (n = 28). •Cortisol: serum. Radioimmunoassay method. •BP: considered as primary outcome. Measured in 4 times by direct measurement (arterial catheter). Other measures: anthropometric data, clinical data, meta and normetamefrin, creatinine, cardiac markers.	Systolic blood pressure increased in patients with Landmark-guided regional anesthesia (RA) compared to patients with general anesthesia (GA) even prior to surgery and remained elevated throughout the surgery but returned to baseline values 1 hour after admission of patients in the postoperative anesthesia unit. They concluded that the US-RA technique for CEA induces temporary intraoperative SAH and an increase in levels of stress hormone including cortisol.
13. Baudrand, et al. Chile, 2014[32] Clinical Endocrinology	To evaluate whether the diet with high sodium content is associated with the dysregulation of cortisol and MetS production.	•Cross-sectional study. •Hispanic adults from low- and middle-income primary health units (n = 370). •Cortisol: salivary, evaluated by immunoassay method. •BP: method of measurement not described. Other measures: anthropometric, metabolic and clinical data, allowing classifying the MetS, consumption of salt (urinary sodium).	High sodium intake is associated with increased urinary cortisol metabolites, insulin resistance, dyslipidemia and lower levels of adiponectin. The results too suggest that a increase in total urinary of glucocorticoids may partially explain the metabolic disturbances observed with a salty diet, in addition to the risk of SAH.
14. James USA, 2014[33] American Journal of Human Biology	To compare levels of urinary catecholamine (epinephrine and norepinephrine), cortisol excretion and ambulatory BP values in three distinct daily microenvironments between women with and without parental SAH.	•Comparative cross-sectional clinical study. •American adult women, (n = 62) working in clinical, technical or professional positions in a medical center. •Cortisol: urinary, evaluated by radioimmunoassay method. •BP: monitored ambulatory BP at the beginning of the workday (between 8 and 9 AM). Other measures: anthropometric, demographic data, medical history, daily stress information, in addition to, epinephrine and norepinephrine.	The associations suggest that there may be genetically linked mechanisms that raise levels of epinephrine and nocturnal levels of cortisol that contribute to elevated circadian BP.
15. Malan et al. South Africa, 2014[34] Journal of Human Hypertension	To assess the association between cortisol levels, psychological stress and BP responses in South African men stratified according to testosterone levels (low and high T).	•Comparative cross-sectional clinical study. •African (n = 94) and Caucasian (n = 100) urban teachers from Northwest South Africa, •Cortisol: serum by immunoassay method. •BP: outpatient BP measurements. Other measures: anthropometric measurements, serum testosterone, mental stress tests, health perception questionnaire, physical activity practice, electrocardiogram (silent ischemia).	The associations of chronic distress (cortisol) and acute stress (total peripheral resistance cold pressure responses) were associated with beat-to-beat and ambulatory blood pressure (ABPM) within the low testosterone (T) in African group. Acute and chronic (cortisol) stress may contribute to increased BP in low T in African men. Their cortisol and vascular responses supported a tendency for ischemia, increasing their risk for coronary artery disease.
16. Jarrete et al. Brazil, 2014[35] Journal of Clinical & Translation Endocrinology	Investigate whether aerobic exercise training (AET) over twenty-four sessions alters the levels of cortisol, leptin, and interleukin-1β (IL-1β).	•Longitudinal study of type clinical trial with before and after evaluation. •Postmenopausal hypertensive women (n=18) submitted to physical training protocol. •Cortisol: serum, evaluated by immunoassay method. •BP: the average of three consecutive measurements. Other measures: lipid profile and glycaemia, leptin, interleukin - 1β and cyclic GMP (cGMP), nitrite - nitrate ratio.	The beneficial effects of exercise training on blood pressure were related to an improvement of NO/cGMP pathway without changing in serum cortisol levels. Were confirmed by the lack of positive correlation between cortisol and blood pressure after twenty-four sessions of exercise. The associations show that the endocrine-inflammatory mediators cortisol, leptin and IL-1b did not contribute to the beneficial effects of the exercise training on blood pressure in hypertensive postmenopausal women.
17. Bennett et al. USA, 2013[36] Stress and Health	To examine the effects of caffeine and psychological stress on markers of cardiovascular disease (CVD) in young adults with a family history of SAH.	•Clinical trial with 2x2 design (sex and caffeine / placebo). •Healthy men (n=26) and women (n=26), young people with a confirmed family history of SAH. •Cortisol: serum, evaluated by immunoassay method. •BP: measured in three times (before, during and after a stress inducing procedure). Other measures: serum estradiol and progesterone, HR, C-reactive protein (CRP) and plasma fibrinogen.	The result from this study suggests that the combination of stress and caffeine may be detrimental for females with a family history of SAH. The stress interacted with caffeine and women, at were alter cortisol, fibrinogen and systolic BP but not CRP levels. These results may on sex - specific pathways that associate caffeine with on blood markers of CVD.

Figure 2. Synthesis of the analyzed studies. 2018.
**pg: picogram; mg milligram*

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Main types of study, methods of clinical analysis and factors those were associated

The main methods of study were cross-sectional and the most frequent clinical analyzes were cortisol obtained through blood (10 studies), most of which were evaluated by immunoassay followed by saliva (4), urine (2) and capillary analysis (1).

Among the associated factors between SAH and cortisol, we observed a population with chronic disease already established, whose related variables are gender, age, family history, ethnicity, anthropometric measures, socio-demographic characteristics, stress questionnaires, mood, health perception, physical activity, sodium and caffeine consumption, electrocardiogram, lipid profile, MetS, insulin, glycemia and others (proteins, hormones, leptin, interleukin, nitrite, nitrate, adrenaline and serum creatinine).

DISCUSSION

The results of this study demonstrated the variety of methods of research and associations between SAH and cortisol. It is known that SAH is a chronic condition that can lead to the development of heart or kidney disease. Thus, based on the scientific evidence, one study pointed out that renal function disorders were associated with the HPA axis with RASS, showing that they are significantly associated with SAH. Renal function parameters such as creatinine and cystatin C (eGFRcr-cys) are related to the high level of cortisol in subjects with SAH.[6,24]

Recent studies have shown that deregulation of the HPA axis together with chronic stress increases the likelihood of SAH, leading to heart disease such as ischemia, a deficit in blood perfusion and stroke-related diseases.[22,23]

In another investigation, it was suggested that healthy individuals with a genetic history of SAH have a marked increase in catecholamines and cortisol for stressors in relation to elevated plasma levels when compared to those with no parental history. The study compared catecholamines by urine (epinephrine and norepinephrine), excretion of cortisol and ambulatory BP in three daily microenvironments between women, with and without parental history of SAH.

The results suggest that there may be genetically linked mechanisms that raise levels of adrenaline and nocturnal levels of cortisol that contribute to elevated circadian BP. However, elderly people with SAH with low levels of cortisol on awakening were related to worse cognitive function.[25,33]

Another factor was the hormone testosterone (T); study indicates that low levels of T, high level of cortisol and chronic stress are associated with SAH. Thus, the authors concluded that acute and chronic stress may contribute to increase cortisol and BP in subjects with low T, contributing to an increased risk of coronary heart disease.[34]

Regarding the women, research examined the interaction between endocrine inflammatory mediators and aerobic exercise training in postmenopausal individuals and individuals with SAH. Thus, it was concluded that aerobic physical exercises produce a significant reduction of BP, however, without altering cortisol and leptin levels.[35]

Another intriguing factor is the effects of caffeine and stress on biomarkers of cardiovascular disease. A total of 52 healthy normotensive adults (26 men and 26 women), but with a family history of SAH, participated in the study to examine the reactivity to stress after caffeine consumption. Subjects after caffeine received increased systolic BP and cortisol. The study suggested that the combination of stress and caffeine may be particularly harmful for women with a family history of SAH.[36]

Another study correlated serum cortisol with cortisone (F/E) and BP with severe obesity before and after weight loss and the alteration of the F/E serum ratio was associated with BP alteration after weight loss.[26]

Patients with Human Immunodeficiency Virus (HIV) are at increased risk for metabolic complications (MetS) including SAH and excess cortisol. In this sense, a study was conducted in the Netherlands where they identified that the risk of MetS was higher in HIV-infected patients in the lower-level capillary cortisol group compared to patients with higher levels. These results contradict those of studies in uninfected individuals, where a high level of capillary cortisol is being associated with MetS.[27]

However, a study with adults relating MetS to the measurements of salivary cortisol levels aimed to verify whether it is affected by the variables age, gender and hormone therapy, estrogen and progestin; the results showed that the older age was related to MetS and cortisol excretion.[28]

In addition, high sodium (HS) diet was associated with increased cortisol in urine and its metabolites, with SAH, insulin resistance (RI), dyslipidemia, hypoadiponectinemia, higher cortisol, leading to metabolic disorders related to obesity.[32]

The results of a study in premenopausal women suggest that not eating breakfast is harmful because it can interrupt the cortisol rhythm and result in altered BP and, consequently, leading to cardio metabolic diseases.[29]

In the hospital area, a study on loco-regional anesthesia was identified, an effective method to evaluate brain function during carotid endarterectomy (CEA). Regional framework-guided anesthesia (RA) is currently used for CEA and may cause substantial perioperative SAH. Ultrasound-guided RA (US-RA) is a new method for performing RA in CEA. The study evaluated early sympathetic activity during CEA in US-RA compared to general anesthesia (GA). Regional ultrasound-guided anesthesia for carotid endarterectomy (CEA) induces early changes in hemodynamic hormone and stress. Thus, systolic BP increased in patients with RA-AR compared to AR, even before the surgery was started, remained elevated during the complete surgery and returned to baseline 1 hour after admission to the anesthesia care unit postoperative period, as well as HR and cortisol levels were also higher in the US-RA group after induction of anesthesia. The authors concluded that the US-RA technique for CEA induces temporary intraoperative SAH and an increase in levels of stress hormone.[31]

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Regarding the types of treatments for the control of SAH, one study presented the physiological effects such as the reduction of BP in "walking in the forest" therapy, as a promising treatment strategy. It is known that SAH requires preventive actions, such as guidelines on life habits, decreased salt intake, physical activities, and the correct use of medications and antihypertensive.[30,37]

The findings of this study reinforce the idea of how cortisol influences SAH, so we can delve into the cause of HPA axis activation and excess cortisol excretion.

This study presents as limitations the different research methods, such as cortisol collections, demographic partner factors, ethnicities and different hormones linked to it, which may influence the association of cortisol with BP elevation.

CONCLUSIONS

The results indicate that the most commonly used clinical methods for linking SAH to cortisol are association tests, performed with renal and / or cardiac function, metabolic syndrome, stress, chronic diseases together with the evaluation of laboratory tests and / or markers and measures anthropometric and physiological.

Previous studies indicate that BP is altered by HPA axis dysregulation, where stress is released into the bloodstream and its effects are possibly malefic. Thus, to help maintain BP levels within the normal range, it is recommended to adopt a healthy lifestyle.

Currently, the major challenge for science is to investigate the pathophysiological processes involved and in which situations the HPA axis secretes the hormone cortisol in excess.

Most of the articles showed a positive association between cortisol and BP, indicating the correlation between them, for several variables: increased cortisol was higher in the elderly (62 years), increased sodium in the diet, not eating breakfast, excessive caffeine during the day, Metabolic Syndrome, obesity, excess catecholamine's, some types of hormones and biomarkers.

Due to the above, there is a need for more clinical research with other methodological approaches, highlighting the role of cortisol in the regulation of BP, in order to investigate the possible causes of the secretion of this hormone in excess and its pathophysiological effects on SAH.

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