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VIEW AND REVIEW

# Basal cortisol levels and the relationship with clinical symptoms in multiple sclerosis: a systematic review

## Níveis de cortisol basal e a relação com sintomas clínicos na esclerose múltipla: uma revisão sistemática

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**ABSTRACT**

Multiple sclerosis (MS) is a demyelinating, progressive and neurodegenerative disease. A disturbance on the hypothalamic-pituitary-adrenal axis can be observed in patients with MS, showing altered cortisol levels. We aimed to identify basal cortisol levels and verify the relationship with clinical symptoms in patients with MS. A systematic search was conducted in the databases: Pubmed, Web of Science and SCOPUS. Both higher and lower cortisol levels were associated with MS. Higher cortisol levels were associated with depression and anxiety, while lower levels were associated with depression, fatigue and urinary dysfunction. Higher cortisol levels may be associated with the progression and severity of MS.

**Keywords:** Multiple sclerosis; hydrocortisone; pituitary-adrenal system; neurologic manifestations; general symptoms.

**RESUMO**

A esclerose múltipla (EM) é uma doença desmielinizante, progressiva e neurodegenerativa. Um distúrbio no eixo hipotálamo-hipófise-adrenal pode ser observado em pacientes com EM, mostrando níveis alterados de cortisol. Nosso objetivo foi identificar os níveis basais de cortisol e verificar a relação com os sintomas clínicos em pacientes com EM. Uma busca sistemática foi realizada nas bases de dados: Pubmed, Web of Science e SCOPUS. Ambos os níveis de cortisol elevado e baixo foram associados com a EM. Níveis mais elevados de cortisol foram associados à depressão e ansiedade, enquanto níveis mais baixos foram associados à depressão, fadiga e disfunção urinária. Níveis altos de cortisol podem estar associados à progressão e gravidade da EM.

**Palavras-chave:** Esclerose múltipla; hidrocortisona; sistema hipófise-suprarrenal; manifestações neurológicas; sintomas gerais.

Multiple sclerosis (MS) is a progressive and inflammatory neurodegenerative disease, characterized by demyelinating lesions and atrophy, in the central nervous system (CNS)[1,2,3]. It affects 1/1,000 people in the western world and leads to chronic disability in young adults ranging between 20 and 40 years old[4]. Multiple sclerosis presents an unpredictable and often progressive course, with many neurological symptoms[5], which include sensory disorders[6], visual problems[7], fatigue[8], alterations in balance[9], dysfunction of the lower urinary tract[10], limitations in walking[11] and cognitive dysfunction[12].

The etiology of MS is considered multifactorial and involves genetic and environmental mechanisms, which affect the immunological response[13]. Although the origin is still unknown, autoimmune mechanisms are considered central triggers of MS[14]. A widely-accepted model considers MS to be an autoimmune chronic inflammation, mediated by T-cells and macrophages infiltrating the CNS through the peripheral immunological system, which is involved in myelin sheath destruction along with microglia[10,15]. Nowadays B-cells are getting a great deal of attention as well.

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It has been demonstrated that alterations in the neuroendocrine system may also be involved in immune suppression or activation, increasing the vulnerability and severity of autoimmune diseases such as MS[4,16,17]. In this context, several studies have indicated that there is a role of the hypothalamic-pituitary-adrenal (HPA) axis in the control of MS progression[18]. In physiological conditions, the HPA axis releases glucocorticoids able to mediate the expression of inflammatory genes of cytokines, action of monocytes and macrophages, and adhesion and migration molecules, which have immunomodulatory effects[19,20]. In patients with MS, activation of the HPA axis appears to be dysregulated, and chronic hyperactivity occurs in about 50% of the patients[14,18,21,22]. The reactivity of the HPA axis has been correlated with MS progression and global increase in the activation of the neurodegenerative process[21,23,24].

Cortisol is an end-product glucocorticoid of the HPA axis in humans, considered to be the stress hormone and a powerful natural immunosuppressant, involved in regulatory functions such as in glucose metabolism, insulin release, arterial pressure, immune and inflammatory responses[4,25]. In MS, as a consequence of the disrupted HPA axis, cortisol levels become altered. In patients with MS, the cortisol response after intravenous administration of corticotrophin-releasing hormone is higher, when compared with healthy adult subjects[26,27,28]. This increase of the cortisol response was associated both positively[29], and negatively[30], with the number of acute lesions due to central neuroinflammation in MS.

In several studies, higher levels of basal cortisol were observed in the cerebrospinal fluid (CSF) and blood, as well as an increase in the cortisol awakening response measured in saliva[5,25,30,31,32,33]. As well, evidence in postmortem humans showed that higher levels of cortisol in the CSF are neuroprotective while lower levels are related to a higher number of lesions[30].

Physiologically, cortisol release levels and the activated cerebral regions depend on the type of stress factor, where motor stress has been associated with brainstem activation while psychological stress has been associated with limbic regions[34]. In MS, some studies have investigated the relationship between cortisol levels and symptoms that arise during the course of the disease; however, there is still no consensus about the role of cortisol as a cause or consequence of the symptoms. Current evidence is directed, mainly, to the relationship of cortisol with fatigue and depression, which are the most common symptoms in MS[35,36].

In affective symptoms, such as anxiety and depression, significant correlations are found with higher levels of cortisol, especially in patients suffering from relapsing-remitting multiple sclerosis (RRMS)[5,29,37]. Furthermore, studies have shown that cortisol is correlated with fatigue and might have an important role in RRMS[25,38]. Nevertheless, contradictory results have also been observed, where MS patients with depression and chronic fatigue showed cortisol levels with no increase or significant correlations[39,40,41].

Even though several investigations have considered the role of the HPA axis in MS, there is still little consensus about the cortisol levels and their role in MS pathophysiology. In this study, we aimed to investigate basal cortisol levels in MS and the methods of cortisol evaluation, though a systematic review. Moreover, we intended to verify whether cortisol levels were related to clinical symptoms observed in multiple sclerosis.

## METHODS

The systematic review was performed on the results of the database searches from January to March in 2018, which were conducted according to PRISMA guidelines[42]. The articles were selected from three databases: PubMed, Web of Science and SCOPUS. To find representative articles, the following keywords were input: [*multiple sclerosis AND cortisol*]; [*multiple sclerosis AND cortisol AND progression*]; [*multiple sclerosis AND stress AND cortisol*]; [*multiple sclerosis AND cortisol AND progression AND stress*].

The selected articles in this review were assessed independently by two evaluators and met the following criteria: 1) the sample comprised only humans ( from 18 years of age); 2) the articles were published between 2006 and 2017; 3) patients had been affected only by MS, with no neurological diseases from other etiologies; 4) cortisol had been assessed from urine, blood, CSF, saliva or hair; 5) there was an assessment of any physical, behavioral and/or cognitive symptom; 6) the full text of the article was available in the database; 7) the full article was in English. Articles were excluded from the sample if: 1) they were review articles, book chapters and abstracts published in journals; 2) they used pharmacological, physical or psychological stimulation as a stressing agent to observe the HPA axis function. Only articles that fulfilled all the requirements were included in this review.

In the initial assessment, only the abstracts of the articles were read. If the data were not enough, the evaluators assessed the methods and results of the articles. Accepted articles that met all the inclusion criteria were read and analyzed comprehensively.

Analysis of the articles was made qualitatively, according to the method of assessment of cortisol and the division of study groups. After analyzing the articles, results were placed in a table with the following information: authors and year of publication, study goals, sample number and groupings, mean age, main results (Table 1). Bias risk was assessed in every article according to the following criteria: sample randomization; cortisol storage duration, temperature, method; assessment kit (Table 2).

Table 1. Characteristics of the studies that assessed basal cortisol levels and their relationship to symptoms of multiple sclerosis (n = 20).

| Authors, year | Objective | Subjects (n) | Groups (n) | EDSS | Age (years) | Assessment | Sample type | Basal cortisol | Main results |
|---|---|---|---|---|---|---|---|---|---|
| Akcali et al., 2017[50] | To compare Fatigue Severity Scale and Neurological Fatigue Index-MS and assess the relation between fatigue and serum biomarkers in patients with MS | 80<br>F= 42<br>M = 38 | MS Fatigued = 26<br>MS Non-fatigued = 28<br>Control = 26 | 1.34 ± 1.09<br>0.98 ± 1.15 | 34.6 ± 8.5<br>33.9 ± 7.4<br>32.4 ± 4.0 | Fatigue Severity Scale, Neurological Fatigue Index-MS, serum IL-1β, TNF-α, IL-35, IL-2, IL-10, ACTH, cortisol, α-MSH, β-MSH, γ-MSH and CLIP | Serum | 22.26 ± 8.43 µg/dl<br>20.90 ± 6.68 µg/dl<br>15.38 ± 9.57 µg/dl | Cortisol levels were elevated in fatigued and non-fatigued patients in comparison to control group. Cortisol was similar in fatigued and non-fatigued patient groups. |
| Villoslada et al., 2017[49] | To identify biomarkers to severity of MS. | 312<br>F = 196<br>M = 116 | MS = 238<br>Control = 74 | 1.5 (0-.5.)<br>2.0 (0-7.5) | 33.6 ± 8.7<br>33.2 ± 4.2 | Retrospective cohort study. Cortisol assessment in the first meeting and 2 years later. | Serum | - | Cortisol levels showed just a trend of association with disability and severity measured two years later. |
| Najafi; Moghadasi, 2017[43] | To assess training effect of yoga on cortisol and ACTH levels in MS females. | 24<br>F = 24 | MS yoga = 14<br>MS control = 10 | 1 to 5.5 | 29 to 50 | 90 minutes of yoga, 3 times a week, for 8 weeks. Assessment done 48h before first training and 48h after last training. | Plasma | 3.56 ± 1.22 µg/dL<br>11.69 ± 1.25 µg/dL | Post-training cortisol levels decreased in comparison to pre-training, also when compared with control group. |
| Melief et al., 2016[24] | To explore prognostic relevance of assessment of GR haplotype and cortisol levels and sCD163 in CSF of patients with MS. | 137*<br>M = 46<br>F = 91 | SPMS = 77<br>PPMS = 34<br>RRMS = 26 | 6.0 | 55 to 78 | Postmortem assessment, CSF from lateral ventricles centrifuged. | CSF | - | Cortisol was correlated with sCD163, especially in GS-L group. There was no correlation of cortisol with time of progress and duration of MS according to EDSS 6,0. |
| Arata; Sternber, 2016[51] | To examine effects from TVAM of the HPA axis in patients with MS and to determine any relationship between the autonomic nervous system function and the HPA axis. | 72<br>M = 26<br>F = 44 | RRMS = 61<br>PPMS = 6<br>SPMS = 5 | - | 49.6 ± 11 | Measurement of cortisol, ACTH, systolic and diastolic pressures, cardiac frequency variability, 24h before and after TVAM. | Serum | 10.7 ± 0.6 pg/ml | Decrease of cortisol and ACTH before TVAM in 18% and 25% of the patients. There was a significant reduction in cortisol levels and ACTH after TVAM. Cortisol was correlated with systolic pressure. |
| Koutsis et al., 2016[52] | To investigate neuroendocrine correlations with bladder dysfunction at the beginning of MS. | 101<br>M = 37<br>F = 64 | Overactive bladder-yes = 15<br>Overactive bladder-no = 86 | 1.93 ± 0.9<br>1.37 ± 1.07 | 33.9 ± 11.4<br>35.3 ± 8.5 | Cortisol sample collected within 12 first months since the first demyelination episode. | Serum | 139 ± 68 ng/ml<br>92 ± 42 ng/ml | Cortisol levels significantly lower in overactive bladder -Yes group. No correlation between cortisol levels and MS duration. |
| Baranowska-Bik et al., 2015[31] | To evaluate cortisol plasma levels and copeptin in recently-diagnosed patients. | 82<br>M = 17<br>F = 65 | MS = 40<br>Control = 42 | 1.56 ± 0.89<br>- | 34.43 ± 8.5<br>32.28 ± 8.1 | Blood samples were collected 8h after overnight fasting. BMI was measured to subdivide groups into lean and overweight/obese individuals. | Plasma | 348.58 ± 158 nmol/l<br>337.04 ± 265.3 nmol/l | Cortisol levels were significantly higher in the MS overweight/obese group in comparison with the overweight/obese controls and MS lean group. There was positive correlation between cortisol and copeptin, and between cortisol and C reactive protein. |

Continue

**Table 1.** Characteristics of the studies that assessed basal cortisol levels and their relationship to symptoms of multiple sclerosis (n = 20). Continuation

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|---|---|---|---|---|---|---|---|---|---|
| Powell et al., 2015[25] | To explore the relationship between cortisol and fatigue in RRMS. | 76<br>M = 14<br>F = 62 | RRMS = 38<br>Control = 38 | 4.3 5 ±1.40<br>- | 41.89 ± 7.53<br>40.34 ± 8.16 | Ecological momentary assessment performed 4 consecutive days in two projects: one based in events (CAR) – collection performed at awakening; 30 and 45 minutes later; based in time (DCS) — 6 quasi-random samples distributed in 1000h and 2000h. | Saliva | 13.57 ± 3.77 nmol/L/min<br>11.78 ± 2.95 nmol/L/min | CAR was higher in RRMS than in the control group. Accumulated fatigue in RRMS was associated with lower cortisol levels at awakening and higher CAR. The CAR was not associated with fatigue on the same day. |
| Eftekhari et al., 2014[44] | To determine if a resistance training program and whole body vibration has any effect on hormone changes in female MS patients. | 24<br>F = 24 | RRMS = 12<br>Control = 12 | 2.87 ± 0.82<br>2.79 ± 0.65 | 35.08 ± 6.89<br>33.75 ± 5.32 | Resistance training and vibration, 3 weekly sessions for 8 weeks. Cortisol was measured before and after intervention, between the 8th and 10th day of the follicular phase of the menstrual cycle. | Serum | 12.32 ± 4.1 ng/ml<br>9.51 ± 3.4 ng/ml | Significant reduction in cortisol concentrations after training in RRMS compared with control group. |
| Melief et al., 2013[30] | To investigate how activity of the HPA axis in MS is related to severity, neurodegeneration, depression, lesions and genic expression in normal-appearing white matter. | 49<br>M = 13<br>F = 36 | - | 3 to 9 | 32 a 83 | Postmortem study. Normal-appearing white matter and hypothalamus were dissected and stored for 30 days. CSF collected to analyze cortisol. Corticotropin-releasing hormone expressing neurons counted. | CSF | 236 nmol/l | Higher cortisol levels are associated with delay in MS progression, above all in women with SPMS. Lower cortisol was related to higher number of active lesions and smaller remyelinated plates, and related to quick progression of MS. No differences in lower and higher cortisol levels with humor disorders. |
| Kern et al., 2013[45] | To measure cortisol daily release, including CAR under basal conditions. | 111<br>M = 46<br>F = 65 | RRMS = 55<br>SPMS = 22<br>Control = 34 | 2.71<br>4.86 | 36.56<br>45.91<br>35.56 | EDSS, CES-D and TICS.<br>Cortisol collected 6 times over 24h (on awakening, 20, 45, 60 minutes later, 3 pm and 10pm, on 2 separate days within 2 weeks. | Saliva | - | Circadian release of cortisol in RRMS was different in the control group. There was no difference in CAR in treated and never treated patients. Follow-up groups with progression of EDSS showed a significant increase in CAR when compared with the controls. Stress and depression did not correlate with CAR in RRMS. |

Continue

**Table 1.** Characteristics of the studies that assessed basal cortisol levels and their relationship to symptoms of multiple sclerosis (n = 20). Continuation

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|---|---|---|---|---|---|---|---|---|---|
| | | 68 | RRMS = 34 (12 PAD; 22 PNAD) | 1.75 (0.0–5.0) | 36.7 ± 7.6 | | | 22.00 lg/dl - 7.30am | |
| Wipfler et al., 2013[46] | To investigate a potential circadian periodicity of expression levels of several cytokines relevant to MS, adhesion molecules and cytokine receptors. | M = 16 | Control = 34 | | | Blood collection at 7am, 11am, 2:30pm, 6pm and 9:30pm. Cortisol. | Serum | 3.60 lg/dl - 9.30 pm | No significant differences in cortisol levels during the day. There was a decrease in cortisol between 7:30am and 9:30pm in both MS groups. Cortisol was higher in PAD if compared to PNAD. |
| | | F = 52 | | - | 36.8 ± 7.2 | | | | |
| | | 48 | RRMS = 32 | - | 30.53 | | | Low BDI 1299.92 ± 394.33 nmol/l | |
| Kern et al., 2011[5] | To examine circadian function of the HPA axis and CAR in patients with RRMS, with maximal duration of 36 months. | M = 11 | Control = 16 | - | 30.37 | CAR assessed on two different days in a week. Sample collected on awakening, 30, 45, 60 minutes later, at 3pm and 10pm. EDSS and BDI. | Saliva | High BDI 1486.40 ± 435.29 nmol/l | RRMS showed higher CAR levels than the control group. Only RRMS patients with moderately higher BDI had different levels compared to controls. |
| | | F = 37 | | | | | | | |
| Gold et al., 2011[37] | To examine the role of the HPA axis activity in subpopulations of T-cells from patients with RRMS and MDD. | 44 | RRMS = 34 | 2.2 ± 0.2 | 35.8 ± 0.7 | Circadian profile collected on 2 consecutive days at awakening, 11am, 3pm, 8pm and 10pm. EDSS and Hospital. | Saliva | - | Patients with MDD showed HPA axis hyperactivity, with elevated cortisol levels at night. No differences observed in CAR between groups. Decrease in cortisol levels was not associated with CAR but was a significant predictor of severity in depression. |
| | | F = 44 | RRMS-MDD = 10 | 3.3 ± 0.3 | 37.2 ± 2.2 | Anxiety and Depression Scale. | | | |
| Lombardi et al., 2011[53] | To investigate the correlation between blood hormones and SD in women of reproductive age with MS. | 55 | MS-SD = 31 | 2.9 (1.5-6) | 34.7 (26-44) | Hormone assessment, including cortisol on the third day of menstrual cycle. FSFI, EDSS. | Serum | 232.14 (180–366) nmol/l | No alteration in cortisol levels in comparison to standard laboratory levels and no correlation with the FSFI. |
| | | F = 55 | EM = 24 | - | - | | | | |

Continue

**Table 1.** Characteristics of the studies that assessed basal cortisol levels and their relationship to symptoms of multiple sclerosis (n = 20). Continuation

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|---|---|---|---|---|---|---|---|---|---|
| Gold et al., 2010[47] | To explore if specific sub-regional volumes of hippocampus can be linked to alterations in daytime cortisol secretion. | 49<br>M = 6<br>F = 43 | RRMS = 29<br>Control = 20 | 2.5 ± 0.2<br>- | 37.5 ± 1.6<br>35.1 ± 1.9 | BDI-II, BAI, MRI of hippocampus, dentate gyrus, subiculum and entorhinal cortex. Diurnal cortisol was collected at awakening, 4pm and 9pm on two consecutive days. | Saliva | - | Patients with RRMS and depressive symptoms showed higher cortisol levels and a smaller CA23DG. The volume of CA23DG was correlated cortisol levels. |
| Heidbrink et al., 2010[48] | To determine DHEA and cortisol levels in CSF and blood of patients with MS, OIND and NIND. | 78<br>M = 33<br>F = 45 | MS = 34<br>OIND = 16<br>NIND = 28 | -<br>-<br>- | 41 (16-65)<br>42 (20-86)<br>49 (22-81) | Blood and CSF collected consecutively between 1pm and 3pm. | CSF and Serum | - | Serum cortisol in MS was just as observed in NIND. CSF cortisol levels in MS were significantly lower. There was positive correlation between MS and OIND in paired CSF and blood analysis. Cortisol levels were lower in CSF and normal in blood during an acute relapse. |
| Mackereth et al., 2009[54] | To compare the effects of muscle relaxing and reflexology training in people with MS. | 50<br>M = 12<br>F = 38 | Group 1 = 25<br>Group 2 = 25 | -<br>- | 48.1 ± 11.06<br>52.5 ± 11.6 | Six weekly session of progressive muscular relaxation; followed by 4 weeks of washout and six-weekly reflexology sessions. SF-36, QHG 28, SAI, cortisol, systolic and diastolic pressure. | Saliva | 7.88 ± 5.35<br>8.49 ± 5.11 | Diminished cortisol levels after one and six weeks. Reduction of anxiety symptoms and systolic pressure. |
| Ysrraelit et al., 2008[32] | To investigate HPA activity in MS subgroups. | 233<br>M = 79<br>F = 154 | PPMS = 40<br>SPMS = 41<br>RRMS = 58<br>RRMS relapse = 34<br>Control = 60 | 4.3 ± 1.6<br>5.6 ± 1.4<br>1.3 ± 1.1<br>2 ± 1.4<br>- | 49.5 ± 12.7<br>51.2 ± 10.1<br>36.8 ± 10<br>37.5 ± 8.4<br>49.0 ± 5.0 | EDSS, BDI, HDS, MFIS. Cortisol, ACTH, DHEAS. | Plasma<br><br><br><br><br><br>Urine<br><br><br><br><br><br> | µg/dL*<br>23.0 ± 7<br>18.4 ± 4.1<br>18.4 ± 5.1<br>24.6 ± 5.5<br>µg/24h<br>348.3 ± 115.6<br>271.8 ± 65.7<br>294.1 ± 7<br>441.5 ± 67.9 | Statistically higher cortisol levels in all groups with MS patients. RRMS relapse group showed higher hyperactivity. There was no correlation between fatigue and depression with cortisol levels. |
| Téllez et al., 2006[40] | To test if fatigue in MS is associated to endocrine biomarkers. | 38<br>F = 25<br>M = 13 | MS with fatigue = 29<br>MS without fatigue = 9 | 6.0 (6.5-4.0)<br>6.0 (6.0-3.5) | 50.1 ± 8.1<br>45.0 ± 7.7 | FSS, cortisol, DHEAS and basal DHEA. | Serum | - | No differences in cortisol levels between groups. |

*104 for cortisol analysis (17 excluded); ACTH: adrenocorticotropic hormone; AUC: area under curve; BAI: Beck's Anxiety Inventory; BDI: Beck's Depression Inventory; BMI: body mass indexCAR: cortisol awakening response; CES-D: Center for Epidemiological Studies Depression scale; CLIP: corticotropin-like intermediate lobe peptide; CSF: cerebrospinal fluid; DCS: diurnal cortisol slope; DHEA: dehydroepiandrosterone; DHEAS: dehydroepiandrosterone sulphate; EDSS: Kurtzke's Expanded Disability Status Scale; F: female; FSFI: Female Sexual Function Index; GS-L: low sensitivity to glucocorticoids; HDS: Hamilton's Depression Scale; HPA: hypothalamic-pituitary-adrenal; IL: interleukin; M: male; MDD: major depression disorder; MFIS: Modified Fatigue Impact Scale; MRI: magnetic resonance imaging; MS: multiple sclerosis; MSH: melanocyte-stimulating hormone; NIND: noninflammatory neurological disease; OIND: other inflammatory neurological disease; PAD: patients with active disease; PNAD: patients with non-active disease; PPMS: primary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SAI: State Anxiety Inventory; SPMS: secondary progressive multiple sclerosis; TICS: Trier Inventory for Chronic Stress; TVAM: transvascular autonomic modulation; µg/dL - µg/24h*: value attributed to MS groups

Table 2. Analysis of methodological quality of bias risk in the selected articles (n = 20).

| Study, Year | Sample randomization | Pharmacologic Therapy | Cortisol storage time | Cortisol storage temperature | Assessment kit |
|---|---|---|---|---|---|
| Akcali et al., 2017[50] | No | Without DMT or corticosteroids – 3 months | - | -80 °C | Electrochemiluminescence Cobas® 8000 modular system |
| Villoslada et al. 2017[49] | Yes | DMT | - | -80 °C | Ultra-high pressure liquid chromatography-MS |
| Najafi; Moghadasi, 2017[43] | Yes | Without corticosteroids – 3 months | - | - | Radioimmunoassay |
| Melief et al., 2016[24] | No | - | - | -80 °C | Radioimmunoassay |
| Koutsis et al., 2016[52] | No | Drug-free | 3 months | -30 °C | Radioimmunoassay |
| Baranowska-Bik et al., 2015[31] | No | Naive | - | -70 °C | Radioimmunoassay |
| Powell et al., 2015[25] | No | Without corticosteroids – 3 months | - | -20 °C | Immunoassay with fluorescent detection |
| Arata; Sternberg, 2016[51] | No | - | - | - | Electrochemiluminescence assay |
| Melief et al., 2013[30] | No | Without corticosteroids – 8 weeks | - | -70 °C | Radioimmunoassay |
| Kern et al., 2013[45] | No | Naive and DMT | - | -20 °C | Immunoluminescence assay |
| Wipfler et al., 2013[46] | No | Without immunomodulatory/ immunosuppressive therapy (3/6 months) | - | - | ELISA enzymatic immunoassay |
| Kern et al., 2011[5] | No | Within DMT/without glucocorticoids – 4 weeks | - | -20 °C | Immunoluminescence assay |
| Gold et al., 2011[37] | No | Without steroid/ immunosuppressive treatment - 4 weeks | - | - | Radioimmunoassay |
| Lombardi et al., 2011[53] | No | Without corticosteroids – 2 months | - | - | Enzymatic immunoassay |
| Gold et al., 2010[47] | No | Without steroids – 3 months | - | -20 °C | Competitive bonding assay |
| Heidbrink et al., 2010[48] | No | Without corticosteroids, immunosuppressants or immunomodulators (3 months) | - | -80 °C | Immunoluminescent assay |
| Mackereth et al., 2009[54] | Yes | - | - | - | - |
| Ysrraelit et al., 2008[32] | No | No steroids, immunosuppressants or immunomodulators (> 6 months) | - | - | - |
| Eftekhari et al., 2014[44] | Yes | Without corticosteroids (6 months) | - | - | - |
| Téllez et al., 2006[40] | Yes | No steroids (6 months)<br>6-methylprednisolone (only 2 patients) | - | -80 °C | Immunoassay with chemiluminescence |

C: Celsius; DMT: disease modifying treatment.

## RESULTS

In the initial screening, using the above-mentioned keywords, 87 articles were found in PubMed, 149 in Web of Science and 103 in SCOPUS, 339 articles in total. Out of these, 208 articles were excluded as they were in more than one database and 97 articles did not meet the criteria, leaving 34 articles eligible for assessment. The final process of selection resulted in 20 articles being included. All the articles assessed basal cortisol levels in patients with MS, but only 13 studied the relationship of cortisol with any symptom present in the course of MS. The selection process is shown in Figure 1.

### Assessment of basal cortisol levels in MS

A total of 20 articles investigated cortisol levels in basal conditions in MS (Table 1). The sample size in MS groups ranged from 24[43,44] to 173[32] individuals, and some studies included control groups without MS[5,25,31,32,45,46,47,48,49]. According to Kurtzke's Expanded Disability Status Scale (EDSS), the severity of disease, when assessed, ranged from 1–6.5 points, in individuals from 29–65 years old. In most of the studies (14/20), the patients had not used glucocorticoids, immunomodulators or immunosuppressors for at least one month and, in only three articles, the patients either had never been subjected to pharmacological treatment or used to receive the conventional treatment.

Generally, the studies had three types of general objectives: to verify the effect of treatment, pretreatment or post-treatment on cortisol levels, excluding articles about pharmacological/psychological induction (n = 4); to describe the relationship between cortisol and MS symptoms (n = 13) or another condition (n = 1); and to observe the HPA axis profile in patients with MS (n = 13).

The results of cortisol levels were divergent, many articles (9/20) found higher cortisol levels in MS groups[5,25,30,31,32,37,45,47,50], while others (4/20) showed lower levels[30,48,51,52] or did not differentiate (3/20) from the control group or laboratory thresholds[24,46,53]. Some articles did not classify higher or

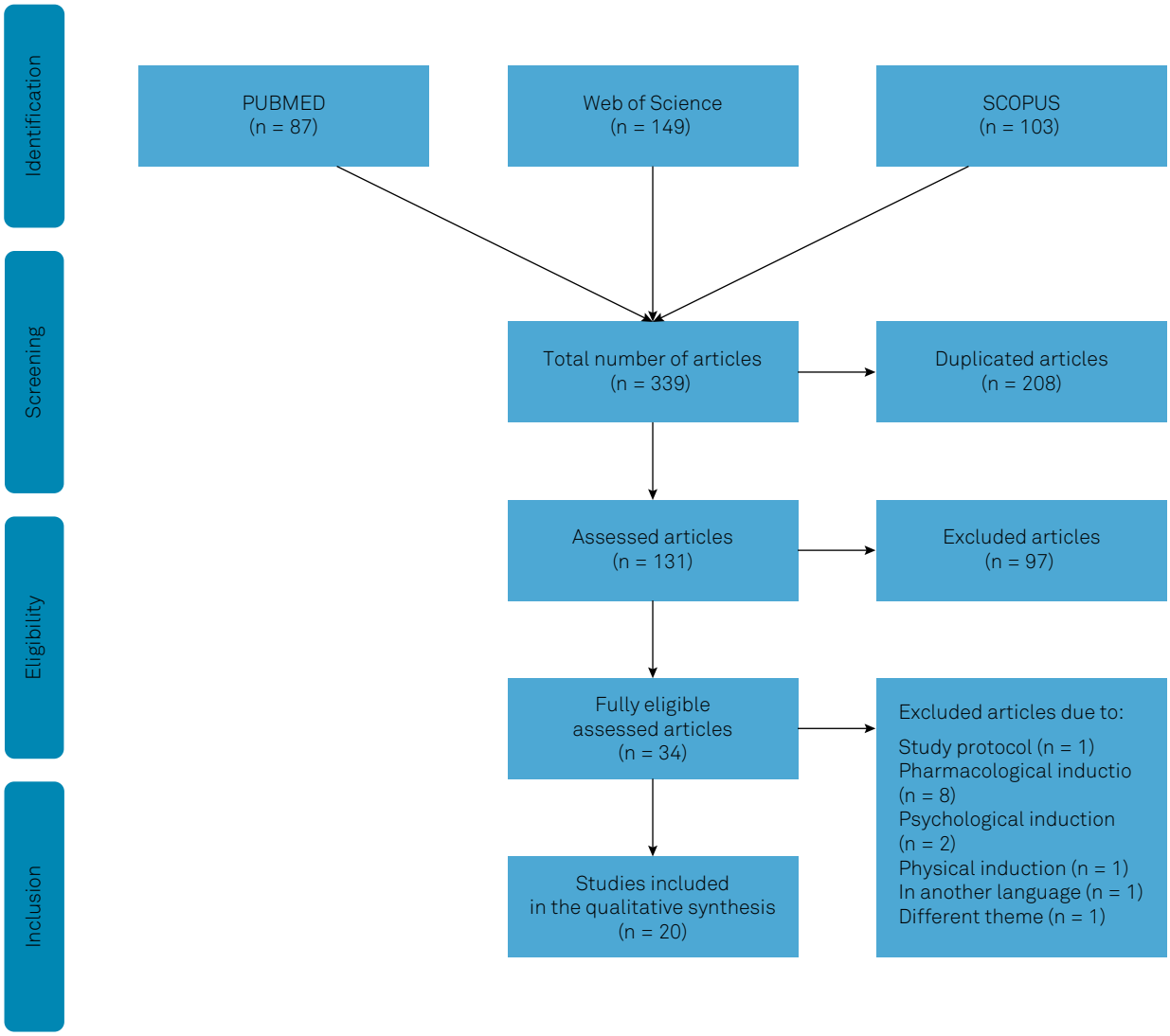


**Figure 1.** Flowchart of the selection process to eligible articles, including the databases: PUBMED, Web of Science and SCOPUS.

lower cortisol levels (4/20), presenting only the treatment effect[43,44,49,54], where there was a reduction in levels after interventions or just the relationship with the symptom (1/20)[40].

Five studies did not show a significant correlation between cortisol levels with the duration, progression or severity of MS[5,24,32,47,52]. One study showed that the cortisol awakening response was associated with the progression of RRMS[45]. There was also a study in which cortisol levels showed a trend to correlation with severity progress in their results[49]. In another study, low cortisol was associated with fast progression and severity of MS[30].

### Types of cortisol samples

Cortisol levels in the articles were assessed from blood, saliva, CSF and urine (Figure 2), while most of the studies used serum samples or blood plasma (60%; n = 12). Two articles performed double sampling of cortisol through plasma/urine[32] and serum/CSF[48], the latter showing a significant difference between the sampling types (CSF: p = 0.0256; serum: p = 0.2886) in different stages of the disease. All the studies that collected saliva investigated the circadian and daytime response of cortisol. No study assessed cortisol from hair samples.

Two postmortem studies included in this review assessed cortisol from CSF and just one ***in vivo*** study performed this type of sampling. Storing temperature, if mentioned, ranged between -30º C and -80° C (Table 2). The most-used method of analysis was radioimmunoassay (31.6%; n = 6) and the least-used methods were the competitive binding assay (5.3%; n = 1), and the ultra-high pressure liquid chromatography with mass spectrometry (5.3%, n = 1).

### Relationship between cortisol and MS symptoms

A total of 13 articles verified the relationship of cortisol levels with symptoms or comorbidities present in patients with MS[5,25,30,31,32,37,40,45,47,50,52,53,54]. The severity of the disease ranged from 1.3–9 points on the EDSS and the age varied from 32–82 years old. The investigated symptoms were depression[5,30,32,37,45,47], fatigue[25,32,40,50], urinary dysfunction[52], female sexual dysfunction[31], anxiety[54] and obesity[31].

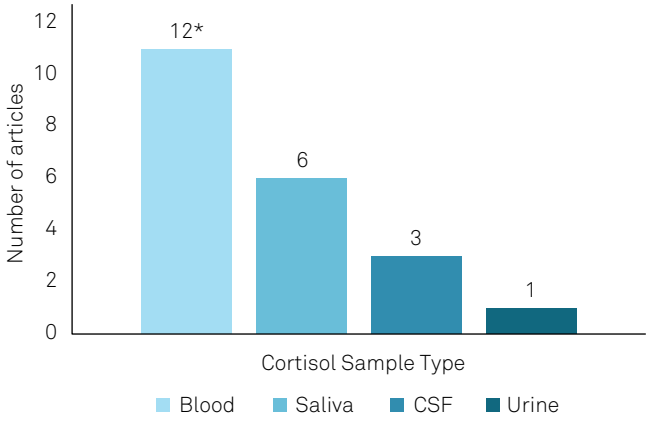


Figure 2. Distribution of articles according to cortisol sample (n = 20). *Includes articles with double sampling[32,48].

The most-assessed symptom was depression and three articles found hyperactivity of the HPA axis, correlating high cortisol levels with depression[5,37,47]. In contrast, other studies (4/20) did not find a correlation between lower[30] or higher[30,32,45] cortisol levels. Next, fatigue was assessed by four articles, which verified a relationship in patients with a low cortisol awakening response[25], high levels of cortisol in patients with fatigue compared to controls[50] or did not observe any relationship between fatigue and cortisol[32,40].

One study found that there may be a reduction of anxiety symptoms associated with lower cortisol levels[54]. Another study did not find a correlation between cortisol and female sexual dysfunction[53], however, lower cortisol levels were related to urinary symptoms in both genders[52]. Finally, overweight patients with MS showed a higher release of cortisol when compared with lean patients[32].

## DISCUSSION

This review included 20 articles, which assessed basal cortisol levels and verified their relationship with any type of symptoms and comorbidities (n = 13) in patients with MS. Those studies assessed cortisol through ***in vivo*** (18/20 studies) and postmortem (2/20 studies) samples. The most-common sample type for assessing cortisol was blood (12/20 studies). Hyperactivity of the HPA axis was observed in most studies (9/20). The most-investigated symptom was depression (6/13 studies). Among the assessed articles, only three found any correlation between cortisol and the duration and progression of MS.

The results found in the various studies in this review support the HPA axis profile in MS, through measuring released cortisol levels. Generally, in most studies, patients with MS showed higher cortisol levels, indicating hyperactivity of the HPA axis, similar to previously-found results[26,27]. Although this impairment can be observed in many cases, its cause-and-effect relationship remains unknown. However, some hypotheses point out its role in affective disorders, such as depression[55], which arises during the course of MS. Thus, depressed patients had higher levels of serum cortisol and this hyperactivity may be related to a decreased response of negative feedback mediated by endogenous glucocorticoids[56].

Alternatively, this hyperactivity of the HPA axis may be linked to the inflammatory activity that happens in active MS. During the inflammatory process, release of cytokines, such as IL-1, IL-6 and TNFα, can perform a modulatory role of the HPA axis, increasing the cortisol release[4]. Alternatively, the HPA axis hypoactivity found in some studies in this review, and decrease in cortisol levels, may be related to the suppression of corticotrophin-releasing hormone neurons that

occurs in active lesion in MS[18]. Furthermore, applying the experimental model of autoimmune encephalomyelitis to animal models of MS has demonstrated that the severity and progression of MS is linked to HPA hyporesponsiveness[57,58].

Additionally, a postmortem study has shown that lower cortisol levels were associated with larger active lesions and fewer remyelinated plates in humans, while higher cortisol levels were associated with a lower number of active lesions and an increase in plate remyelination[30]. From this perspective, hyperresponsive patients showed fewer lesions highlighted by gadolinium, suggesting a neuroprotection of acute lesions[59].

Controversially, the HPA axis hyperresponsiveness in MS may be associated with atrophy in the ***cornu ammonis*** and dentate gyrus in the hippocampus[47], and its relationship with symptoms found in MS[5,31,37,47]. Besides this, patients with exacerbations of RRMS have been shown to have higher cortisol levels compared with healthy subjects[45]. As well, lower cortisol levels were found during the acute relapse than in the stable stage of MS[48].

In this systematic review, many of the studies did not find any relationship between cortisol and MS duration, progression or severity; however, a remarkable number of previous studies have found a relationship between HPA dysfunction and MS progression[18,21,29,59]. The lower cortisol levels found in this review were correlated with the progression of MS, contradicting the fact that lower levels were correlated with more brain lesions[30].

Although these studies preferentially collected blood serum or plasma, this type of sampling only accounts for acute levels of cortisol release, relative to urine, saliva and CSF samples. Moreover, blood and saliva samples provide a momentary profile, while urine samples refer to cortisol levels over a 24-hour period[60]. However, higher cortisol levels found in studies with CSF samples might have been influenced either by the stress generated in response to lumbar puncture or, in postmortem studies, by the response of the HPA axis to the death process[33,48].

Cortisol responses found in these articles refer to acute measurements of the hormone. An alternative to minimizing the interference of stress responses generated by some factors in an ambulatory assessment might be a noninvasive gathering of hair samples. This type of sampling has been considered a reliable method of measuring levels months after exposure to cortisol and it is not influenced by acute stress. Also hair samples can be stored at room temperature[60].

The difference found between the blood serum sample and the CSF in the results can be explained either by the lower activation of cortisone through 11β-hydroxysteroid dehydrogenase type 1 or by inactivation via 11β-hydroxysteroid dehydrogenase type 2[48], or can be regulated by the efflux of cortisol from the brain, which provides a balance to cortisol levels in blood and CSF[61]. In contrast, the similarity in levels found between plasma and urine[32] might occur as both sample types provide cortisol levels in the peripherals.

Articles that described assessment characteristics and sample storage did this according to instructions provided by manufacturers of the respective commercial kits. Nevertheless, many studies did not clarify the duration of storage and did not use sample randomization, which made comparison of results among the studies and validity of processing more difficult and increased the bias risk. Similarly, the choice of an accurate and systematic recruitment in case control studies needed to be obtained in the light of data of healthy individuals and patients without MS, who presented for an investigated condition, such as depression. Furthermore, results in some articles were just described as higher or lower, without ever showing mean values found in each group.

Different symptoms are found in MS and they generally tend to worsen as the disease advances. Fatigue is the most common and debilitating symptom, present in more than 80% of the patients with MS[62]. Although it is regarded as a residual symptom of depression[63], the involvement of cortisol levels remains unclear[25]. The main results encountered in this review on MS did not find any relationship between cortisol and fatigue, corroborating previous evidence that did not observe an influence of cortisol on the fatigue experienced by the patients[39].

Excessive cortisol in the blood has been related to mood disorders[64], such as anxiety and depression. Cortisol performs a central role at the onset and during the course of major depression disorder, where higher basal cortisol levels may be found[65]. Patients with MS who had HPA axis hyperactivity may be susceptible to developing depression[66]. In fact, it has been observed that symptoms of depression may precede the onset of specific neurological symptoms during the initial process of MS; however, in spite of the involvement of several epigenetic factors, the etiology of the depression is multifactorial and varies among patients[67]. In this context, higher cortisol levels found in those studies in patients with MS who had anxiety and depression symptoms may have been related to a hyperresponsiveness of the HPA axis found in mood disorders. The lack of correlation with cortisol levels in some studies may have been due to the methodological design and the materials of investigation employed to classify and assess the depressive disorder.

The lower cortisol levels found in urinary dysfunction may indicate a relationship between the hormones of the HPA axis and the deficit of bladder activity inhibition[52]. Results on the relationship between higher cortisol levels and obesity are controversial, and may be justified by several confounding factors that influence cortisol concentration, such as the increase of ACTH release due to copeptin production or the metabolic activity due to the increase of adipose tissue[31].

One of the limitations of this review is the heterogeneity of the included articles. In fact, there was wide methodological variability, including controlled and uncontrolled studies, as well as randomized and non-randomized essays. Furthermore, the low number of selected articles and the variability of the

sample types may have distorted the interpretation and involvement of cortisol with symptoms in MS. Finally, this review did not include a cohort study that evaluated long-term cortisol in patients with MS, for further understanding of its involvement in the progression of the disease.

In conclusion, this systematic review included an overview of studies that investigated basal cortisol levels and symptoms in MS. The results found pointed to a cortisol level dysfunction and some involvement with symptoms, mainly depression, present in MS. Although there was a satisfactory number of studies and promising investigations on the subject, the results still did not present a consensus on the activity of the HPA axis and cortisol release in patients with MS. However, the majority of studies indicated higher cortisol levels associated with the progression and severity of MS. Differences related to the type of sample were found among both peripheral and central samples, though the number of studies was not enough to clarify the validity and differences among the sample types. The divergences found were limited to lack of methodological consistency, sample size and standardization, such as, for example, the duration of the disease and type of MS, as well as the evaluation types used in some studies. Because of this, further investigations are necessary to better understand the role of cortisol in MS, such as: (1) observation of the cortisol release in peripheral and central samples; (2) verification of the role of cortisol as a trigger for relapses and several motor, cognitive and behavioral symptoms that arise with the disease; and (3) elaboration on standardized methods that control the influence of the circadian cycle on this hormone.

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