

A New Diagnostic Biomarker for Multiple Sclerosis Patients: Endocan Level

Multipl Skleroz Hastalarında Yeni Bir Tanısal Biyobelirteç: Endokan Düzeyi

Filiz DEMİRDÖĞEN¹



¹Atatürk University, Faculty of Medicine, Department of Neurology, Erzurum, Türkiye

Nuray BİLGE¹



¹Atatürk University, Faculty of Medicine, Department of Neurology, Erzurum, Türkiye

Ömer Faruk ODABAŞ²



²University of Health Sciences Konya City Hospital, Department of Neurology, Konya, Türkiye

Turan AKDAĞ³



³Necmettin Erbakan University, Meram Vocational School, Konya, Türkiye

Ali Ulvi UCA⁴



⁴Necmettin Erbakan University Faculty of Medicine, Department of Neurology, Konya, Türkiye

Mustafa ALTAŞ⁴



⁴Necmettin Erbakan University Faculty of Medicine, Department of Neurology, Konya, Türkiye

Recep YEVGİ¹



¹Atatürk University, Faculty of Medicine, Department of Neurology, Erzurum, Türkiye

Çalışma daha önce 27. World Congress of Neurology'de (12-15 Ekim 2025, Seul, Güney Kore) poster olarak sunulmuştur.

The study was previously presented as a poster at the 27th World Congress of Neurology (October 12-15, 2025, Seoul, South Korea).

Geliş Tarihi/Received 25.02.2026
Revizyon Talebi/Revision Requested 19.03.2026
Son Revizyon/Last Revision 03.04.2026
Kabul Tarihi/Accepted 08.04.2026
Yayın Tarihi/Publication Date 16.04.2026

Sorumlu Yazar/Corresponding author:

Filiz DEMİRDÖĞEN

E-mail: fdemirdogen24@gmail.com

Cite this article: Demirdöğen F, Bilge N, Odabaş FÖ, et al. A New Diagnostic Biomarker for Multiple Sclerosis Patients: Endocan Level. *ACMES*. 2026;1(1):23-28.



Content of this journal is licensed under a Creative Commons Attribution-Noncommercial 4.0 International License.

ABSTRACT

Objective: Multiple sclerosis (MS) is an immune-mediated demyelinating disease affecting the human central nervous system. Many molecules are involved in its pathophysiology and help determine prognosis. The goal of this study was to determine serum endocan levels in patients with inactive MS.

Methods: A total of 96 participants were included in the study; 48 patients with relapsing-remitting MS (mean age: 37.46±12.53, 20 men/28 women) and 48 controls (mean age: 38.22±18.57, 22 men/26 women). After the samples were thawed under appropriate conditions, serum endocan levels were analyzed by enzyme-linked immunosorbent assay. The relationship between endocan levels and the Expanded Disability Status Scale, demographic characteristics and medications were analyzed.

Results: The endocan concentration was 371.04±67.39 ng/l in patients with MS and 1003.78±110.63 ng/l in the controls. Patients with MS had significantly lower levels of endocan than the controls did ($P=.003$). Endocan had the lowest diagnostic value (AUC=0.67, (95% CI, 0.56-0.78) as the cut-off value (229.50), sensitivity (63.04%) and specificity (39.13%) in the MS group. In this study, no significant differences were detected between Endocan and the other clinical parameters.

Conclusion: According to the results of our study, compared with those in healthy patients, endocan levels in MS patients were lower. It was concluded that the endocan level can be used as a biomarker in MS patients.

Keywords: Diagnostic biomarker, EDSS, endocan, inflammation, multiple sclerosis

ÖZ

Amaç: Multipl skleroz (MS), insan merkezi sinir sistemini etkileyen, immün aracılı demiyelinizan bir hastalıktır. Patofizyolojisinde rol alan ve prognozun belirlenmesine yardımcı olan birçok molekül bulunmaktadır. Bu çalışmanın amacı, inaktif MS hastalarında serum endokan düzeyini ve bunun patogenezdaki rolünü belirlemektir.

Yöntemler: Çalışmaya toplam 96 katılımcı dâhil edildi; bunların 48'i relapsing-remitting MS hastası (ortalama yaş: 37,46±12,53; 20 erkek/28 kadın) ve 48'i kontrol grubuydu (ortalama yaş: 38,22±18,57; 22 erkek/26 kadın). Uygun koşullar altında çözdürüldükten sonra serum endokan düzeyleri, enzim bağlı immünosorbent analiz (ELISA) yöntemi ile analiz edildi. Endokan düzeyleri ile Genişletilmiş Özürüllük Durum Ölçeği (EDSS), demografik özellikler ve kullanılan ilaçlar arasındaki ilişki değerlendirildi.

Bulgular: Endokan düzeyleri MS hastalarında 371,044±67,396 ng/L, kontrol grubunda ise 1003,783±110,634 ng/L olarak ölçüldü. MS hastalarında endokan düzeyleri kontrol grubuna göre anlamlı derecede daha düşüktü ($P=.003$). Endokan için tanısal değer; eğri altındaki alan (AUC)=0,677 (%95 GA: 0,567–0,787), kesim değeri 229,500, duyarlılık %63,04 ve özgüllük %39,13 olarak saptandı. Çalışmada endokan ile diğer klinik parametreler arasında anlamlı bir fark bulunmadı.

Sonuç: Çalışmamızın sonuçlarına göre, MS hastalarında sağlıklı gruba kıyasla endokan düzeylerinde azalma olduğu gözlenmiştir. Endokan düzeyinin MS hastalarında bir biyobelirteç olarak kullanılabileceği sonucuna varılmıştır.

Anahtar Kelimeler: Tanısal biyobelirteç, EDSS, endokan, inflamasyon, multipl skleroz

INTRODUCTION

Multiple Sclerosis (MS) is disease affecting 2.8 million people worldwide¹, affecting central nervous system, causing widespread neurodegeneration and demyelination in gray and white matter², and impairing quality of life.^{2,3} MS is diagnosed in 2.1 out of every 100,000 people annually. Despite the MS diagnostic criteria, the rate of misdiagnosis is approximately 20%.⁴ Approximately 40% of those diagnosed correctly experience delays in diagnosis and treatment.⁵ While misdiagnosis leads to costs with incorrect drug use, late diagnosis leads to delays in treatment. Delays in treatment lead to a decrease in the duration of approximately 20 years⁶ from the first clinical signs of relapsing remitting MS to the onset of secondary progressive multiple sclerosis (SPMS).⁷ Therefore, many biomarkers and inflammatory molecules have been studied for early diagnosis and disease prognosis.

In the pathophysiology of MS, specific proinflammatory molecules, including interleukin (IL)-1 β , IL-6, IL-8, tumor necrosis factor (TNF), and interferon-gamma are released from autoreactive immune cells, and promote the infiltration of immune cells through the blood–brain barrier, leading to demyelination and axonal damage.⁸ Following the initiation of the inflammatory process, B cells contribute to antigen presentation to T cells and induce the release of cytotoxic mediators that can damage oligodendrocytes. Microglia and macrophages secrete various cytokines, including tumor necrosis factor (TNF)- α and interleukin (IL)-1 β , leading to neurodegeneration through cytokine-induced cell death, inhibition of astrocytic glutamate uptake, and induction of dysfunctional ribonucleic acid-binding proteins. Additionally, the release of glutamate, contributes to glutamate excitotoxicity and subsequent neurodegeneration. Moreover, vascular endothelial growth factor (VEGF), whose expression is elevated in MS lesions, also appears to play a significant role in the pathophysiology of MS.⁹ Endocan is one of the molecules studied for its role in the severity and prognosis of inflammatory disease.

Endocan is secreted by vascular endothelial cells. Endocan is regulated by various proinflammatory cytokines. It is a mature protein of 165 amino acids and a proteoglycan consisting of a 15-40 kDa chondroitin/dermatan sulfate glycan chain that covalently binds to the protein at serine 137.¹⁰ Sarrazin et al.¹¹ reported that endocan cloned from a human endothelial cell DNA library was secreted by epithelial cells of the kidney distal tubules, bronchi, lung submucosal glands, vascular endothelial cells, and other endothelial cells. Endocan is known as a molecule specific to human endothelial cells. It inhibits leukocyte function (leukocyte diapedesis) by interacting with intercellular adhesion molecule (ICAM)-1 through binding to human

leukocytes via integrin leukocyte function-associated antigen-1.¹²

Approximately 1 ng/l of endocan, which is not associated with the endothelial glycocalyx like other proteoglycans are, circulates freely in the circulation.¹³ Blood endocan levels are regulated by de-novo synthesis and secretion.¹⁴ Although the catabolism of endocan is not known precisely, two pathways are thought to be involved: proteolytic degradation by neutrophil cathepsin G and elimination of endocan through hepatic metabolism.^{15,16}

High levels of endocan have been detected in the cytoplasm of vascular endothelial cells in various tumor pathologies such as lung, brain, kidney, ovarian and liver tumors.¹⁷ Endocan levels have also been investigated in cardiac and cardiopulmonary surgeries¹⁸, in patients with Alzheimer's disease¹⁹, in patients with sarcoidosis²⁰, in a control group of 15 adults who died as a result of traffic accidents or falls from height, in patients with grade 1 meningioma and glioblastoma multiforme²¹, and in patients with vasculitis and rheumatologic diseases.²² In this study, we focused on determining the endocan level in multiple sclerosis patients.

METHODS

Forty-eight MS patients in remission diagnosed with the McDonald's criteria for relapsing-remitting multiple sclerosis (RRMS) were included in the study. Forty-eight healthy participants were included. The control group included those who did not have thyroid disease, endocrinopathy, chronic heart or kidney failure, mental illness, known neurological disease, cardiovascular disease, diabetes, or pregnancy. Patients who had not experienced an attack during the past 3 months, who had not received methyl prednisolone treatment, and who had no active plaque on magnetic resonance imaging during the past 3 months were selected. We recorded the participants' sex, age, attacks, and expanded disability status scale (EDSS) score. Blood samples were collected in anticoagulant-free tubes and centrifuged at 2000 rpm (20 minutes at 4°C). The samples were frozen and stored at -80°C. The ethical approval number of the study was Necmettin Erbakan University Medicine Faculty, Turkey Ethics Committee protocol date: April, 27, 2020, number: 14567952-050/56-2020. All participants provided written informed consent prior to enrollment in the study.

Serum concentrations of endocan were assessed by an immunoenzymatic method with a commercially available enzyme-linked immunosorbent assay (ELISA) kit: Human Endocan Elisa Kit: (standard curve range: 0.05 ng/l-10 ng/l, sensitivity: 0.02 ng/l, intra-assay coefficient of variation (CV): 8%; inter-assay CV: 10%; catalog no. E3919Hu, Bioassay Technology Laboratory, Shanghai, China), and the

manufacturers' instructions were followed. The absorbances of the samples were measured by microtiter plate at 450 nm (ELx800TM, BIO-TEK instruments, USA), and the levels endocan are expressed in units of ng/l.

Statistical Analysis

Statistical Package for the Social Sciences version (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. The Mann-Whitney U-test was used to test the statistical significance of the difference between the variables studied. Correlations were performed using Spearman's rank correlation coefficient. Statistical significance of the data expressed as mean±standard deviation (SD) was defined as $P < .05$.

RESULTS

In this study, the mean ages of the 48 patients with MS and the 48 controls were 38.23 and 37.56 years, respectively. All the demographic characteristics of the controls and MS patients are shown in Table 1. Serum endocan levels were significantly lower in patients with MS than in those without MS ($P = .001$). No significant correlation was found between the number of attacks and disease duration, EDSS score and endocan levels (Table 2). We show cutoff and area under the curve (AUC) values of serum endocan levels in MS patients in the Table 3.

Table 1. Serum Endocan Levels in MS and Healthy Group

Parameter	MS group	Healthy group	P
Age (year), mean	37.46±12.53	38.22±18.57	-
Sex, (n)			
Male	20 (39.24%)	20 (39.24%)	-
Female	28 (60.76%)	28 (60.76%)	
Endocan, (ng/l)			.001
Mean	371.04	1003.78	
n	48	48	
Standart deviation	67.39	110.63	

DISCUSSION

MS is a demyelinating disease in which many cytokines play a role in the pathogenesis of demyelination, remyelination stages and inflammation.⁶ Endocan is expressed by some growth factors and cytokines. in the

Table 2. Correlation of Serum Endocan Levels and Some Clinical Findings in MS Patients

Parameter	Endocan	Mean	Standard deviation
EDSS	0.29	1.94	1.84
Medication	0.12	-	-
Number of attacks	0.31	-	-
Disease time	0.11	8.86	6.25

vascular endothelium. High levels of TNF- α , which is present in the serum and CSF of MS patients, plays anplay important roleroles in the pathogenesis of MS²³ and upregulate endocan expression in endothelial cells.²⁴ Increased inflammation causes oxidative stress and endothelial damage. Oxidative stress increases the permeability of the blood-brain barrier.²⁵ In another study conducted by Akil et al.²⁶ in RRMS patients, the endocan level, C-reactive protein level neutrophil-lymphocyte ratio levels were found to be high. In an acute lung injury model (induced by mouse endotoxin (LPS), endocan treatment decreased TNF- α , IFN- γ , IL-6 and IL-1 β leves and inflammatory cytokine levels and attenuated pulmonary epithelial apoptosis.²⁷ This study reveald that high endocan levels may be protective. In a study by Atalar et al.²⁷ endocan levels were found to be high in RRMS patients, while C-Reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR) and endocan leves were not significantly correlated.

The neuroprotective effects of hepatocyte growth factor (HGF), have been observed in various neurodegenerative disease models, including those of Amyotrophic Lateral Sclerosis (ALS), brain ischemia, spinal cord injury, Alzheimer's and Parkinson's disease²⁸ and in vitro and in vivo studies have shown that HGF contributes to regeneration by stimulating axonal growth.²⁹ HGF, which increases the regulatory T cells response and decreases the pathogenic t cell response³⁰, induces proliferation and migration of oligodendroglial progenitor cells³¹ and inhibits the apoptosis of oligodendrocytes³² all of this findings may explain why the leve of endocan, which increases HGF levels, is low in MS patients. Endocan levels were also low in our study. In our study, serum endocan levels were lower in the patient group than in the control group.

Endocan is thought to be a significant regulator of cellular adhesion, cancer development and inflammatory disorders.¹² Endocan plays a considerable role in vascular permeability and pathological angiogenesis.³³ In a study by Rocha et al.³³, the tumor angiogenesis and cerebral edema

Table 3. Cutt-off and Area Under Curve (AUC) Values of Serum Endocan Levels in MS Patients

Factor	AUC (95%, CI)	Cutoff, According to Youden's Index	P	Sensitivity (%)	Specificity (%)
Endocan, ng/l	0.67 (0.56-0.78)	229.50	0.003	63.04	39.13

decreased by 50% in endocan knockout mice after vascular permeability caused by ischemic stroke was decreased. In conclusion, endocan may be used to assess the prognosis and activity of both inflammatory diseases. In this context, a literature review revealed that serum endocan levels are a reliable markers for the diagnosis of various diseases and post treatment responses.³³ However, in our study, no relationship between endocan and EDSS score was found in MS patients.

Zhang et al.³⁴, reported that the levels of interleukin (IL)-6, Tumor Necrosis Factor (TNF)- α , interleukin (IL)-1 β , and interferon (IFN)- γ , levels decreased with endocan treatment and as a result, pulmonary epithelial apoptosis decreased. In a studies, it has been shown that endocan potentiates the mitogenic effects of HGF on endothelial cells and thus wound repair and cell proliferation.³⁵ The proangiogenic molecules vascular endothelial growth factor-A and VEGF-C, which have been shown to be important in angiogenesis and cancer progression, strongly upregulate endocan expression.³⁶ Kul et al.³⁷ reported a positive correlation between VEGF and TNF- α levels and serum endocan levels in patients with Behçet's disease. Recent studies have shown that in experimental autoimmune encephalitis patients and MS patients, VEGF-A mRNA levels in both glial tissue and CSF are lower in mononuclear cells than in controls.³⁸ Iacobaeus et al.³⁸ found a three fold decrease in VEGF-A mRNA expression in CSF cells in RRMS and an eight-fold decrease in SPMS matched controls, but no correlation with sex, the EDSS score or disease duration. In our study, endocan levels, which have been shown to be correlated with VEGF-A levels in previous studies, were lower in the patient group than in the control group. In addition, a relationship between serum endocan levels and disease duration was not found in our study.

The results of the same study by Iacobaeus et al.³⁸ suggest that the low level of VEGF-A mRNA expression in peripheral blood mononuclear cells, particularly in progressive MS, may reflect an underlying disease mechanism. Therefore, VEGF-A can protect neurons from apoptosis-induced environmental stress and directly stimulate axonal regeneration and neurogenesis.³⁹ On the basis of these data, it can be concluded that endocan, which is positively correlated with VEGF-A, is also involved in neurogenesis-axonal regeneration and may be a marker for the transition to progressive MS. If proven by experimental studies, it may be a possible target for modulatory drugs in the future. In addition, the transition to the progressive

phase can be detected early and targeted therapies can be started without delay.

VEGF-C protein, which plays an important role in the development of meningeal lymphatic vessels (MLVs), is expressed by vascular smooth muscle cells.⁴⁰ The plasticity and regenerative potential of the MLV and central nervous system drainage have been studied in the context of neurodegenerative diseases such as multiple sclerosis, dementia, stroke, hydrocephalus and Alzheimer's disease. As shown in our study, low levels of endocan in MS patients may play a role in the development of the MLV together with VEGF-C, with which it increases and decreases in correlation.

CONCLUSION

Endocan levels were found to be low in MS patients. In conclusion, the effects of endocan, which effects on the glymphatic pathway, may open a new avenue for new treatment strategies. However, more detailed and experimental studies are needed.

Veri Paylaşım Beyanı: Bu çalışmanın bulgularını destekleyen veriler, makul bir talep üzerine ilgili yazardan temin edilebilir.

Etik Komite Onayı: Etik kurul onayı Necmettin Erbakan Üniversitesi Yerel Etik Kurulu'ndan (Tarih: 27 Nisan 2020, Sayı: 14567952-050/56-2020) alınmıştır.

Hasta Onamı: Çalışmaya katılan tüm katılımcılardan onam alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir-F.D., Ö.F.O., A.U.U.; Tasarım- N.B., Ö.F.O.; Kaynaklar- F.D., R.Y.; Malzemeler- F.D.; Analiz ve/ veya Yorum- F.D., Ö.F.O., A.U.U.; Yazıyı Yazan- F.D., Ö.F.O., A.U.U., T.A., M.A.; Eleştirel İnceleme- F.D., Ö.F.O., A.U.U., T.A., M.A.

Çıkar Çatışması: Bu makalenin yazarı Nuray Bilge, makale gönderildiği sırada derginin Bölüm Editörü olarak da görev yapmaktaydı. Bu durum potansiyel bir çıkar çatışması oluşturmaktadır. Çift kör hakem değerlendirme süreci uygulanmış ve yazarın editörlük rolü hakemlere açıklanmamıştır. Değerlendirme sürecinin tüm aşamaları, derginin etik politikalarına ve COPE ve ICMJE dahil olmak üzere uluslararası etik yönergelerine uygun olarak gerçekleştirilmiştir.

Finansal Destek: Yazarlar, bu çalışma için finansal destek almadığını beyan etmiştir.

Yapay Zeka Kullanımı: Yazarlar bu çalışma için hiçbir yapay zeka programından yararlanılmadığını beyan etmiştir.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Committee Approval: Ethics committee approval was obtained from Necmettin Erbakan University Local Ethics Committee (Date: April 27, 2020, Number: 14567952-050/56-2020)

Informed Consent: Informed consent was obtained from all participants in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.D., Ö.F.O., A.U.U.; Design- N.B., Ö.F.O.; Resources- F.D., R.Y.; Materials- F.D.; Analysis and/or Interpretation- F.D., Ö.F.O., A.U.U.; Writing Manuscript-F.D., Ö.F.O., A.U.U., T.A., M.A.; Critical Review- F.D., Ö.F.O., A.U.U., T.A., M.A.

Conflict of Interest: The author of this article, Nuray Bilge, was also serving as a Section Editor of the journal at the time of submission. TA double-blind peer-review process was applied, and the author's editorial role was not disclosed to the reviewers. All stages of the evaluation process were conducted in accordance with the journal's ethical policies and international ethical guidelines, including those of COPE and ICMJE.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of Artificial Intelligence: The authors state that no artificial intelligence programs were used for this study.

REFERENCES

- Walton C, King R, Rechtman L, et al. Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS, third edition. *Mult Scler*. 2020;26:1816-1821.
- Lassmann H, Brück W, Lucchinetti CF. The immunopathology of multiple sclerosis: an overview. *Brain Pathol*. 2007;17:210-218.
- Baecher-Allan C, Kaskow BJ, Weiner HL. Multiple sclerosis: mechanisms and immunotherapy. *Neuron*. 2018;97:742-768.
- Kaisey M, Solomon AJ, Luu M, Giesser BS, Sicotte NL. Incidence of multiple sclerosis misdiagnosis in referrals to two academic centers. *Mult Scler Relat Disord*. 2019;30:51-56.
- Kelly SB, Chaila E, Kinsella K, et al. Multiple sclerosis, from referral to confirmed diagnosis: an audit of clinical practice. *Mult Scler*. 2011;17:1017-1021.
- Dendrou CA, Fugger L, Friese MA. Immunopathology of multiple sclerosis. *Nat Rev Immunol*. 2015;15:545-558.
- Nylander A, Hafler DA. Multiple sclerosis. *J Clin Invest*. 2012;122:1180-1188.
- Göbel K, Ruck T, Meuth SG. Cytokine signaling in multiple sclerosis: lost in translation. *Mult Scler*. 2018;24:432-439.
- Su JJ, Osoegawa M, Matsuoka T, et al. Upregulation of vascular growth factors in multiple sclerosis: correlation with MRI findings. *J Neurol Sci*. 2006;243:21-30.
- Kuhle J, Malmeström C, Axelsson M, et al. Neurofilament light and heavy subunits compared as therapeutic biomarkers in multiple sclerosis. *Acta Neurol Scand*. 2013;128:e33-e36.
- Sarrazin S, Lyon M, Deakin JA, et al. Characterization and binding activity of the chondroitin/dermatan sulfate chain from Endocan, a soluble endothelial proteoglycan. *Glycobiology*. 2010;20:1380-1388.
- Bécharard D, Gentina T, Delehedde M, et al. Endocan is a novel chondroitin sulfate/dermatan sulfate proteoglycan that promotes hepatocyte growth factor/scatter factor mitogenic activity. *J Biol Chem*. 2001;276:48341-48349.
- Sarrazin S, Adam E, Lyon M, et al. Endocan or endothelial cell-specific molecule-1 (ESM-1): a potential novel endothelial cell marker and a new target for cancer therapy. *Biochim Biophys Acta*. 2006;1765:25-37.
- Scherpereel A, Depontieu F, Grigoriu B, et al. Endocan, a new endothelial marker in human sepsis. *Crit Care Med*. 2006;34:532-537.
- Gaudet A, Chenevier-Gobeaux C, Parmentier E, et al. Endocan is a stable circulating molecule in ICU patients. *Clin Biochem*. 2017;50:870-877.
- Bécharard D, Meignin V, Scherpereel A, et al. Characterization of the secreted form of endothelial-cell-specific molecule 1 by specific monoclonal antibodies. *J Vasc Res*. 2000;37:417-425.
- Caires NDF, Legendre B, Parmentier E, et al. Identification of a 14 kDa endocan fragment generated by cathepsin G, a novel circulating biomarker in patients with sepsis. *J Pharm Biomed Anal*. 2013;78-79:45-51.
- Bouglé A, Allain PA, Favard S, et al. Postoperative serum levels of Endocan are associated with the duration of norepinephrine support after coronary artery bypass surgery. *Anaesth Crit Care Pain Med*. 2018;37:656-570.
- Varan HD, Guner G, Kizilarslanoglu MC, et al. Higher serum endocan level is associated with Alzheimer disease. *Dement Geriatr Cogn Disord*. 2017;44:303-310.
- Aciksari G, Kavas M, Atici A, et al. Endocan levels and endothelial dysfunction in patients with sarcoidosis. *Angiology*. 2018;69:878-883.
- Atukeren P, Kunbaz A, Turk O, et al. Expressions of endocan in patients with meningiomas and gliomas. *Dis Markers*. 2016;2016:7157039.
- Yilmaz Y, Berru Durmuş R, Saraçoğlu B, et al. The assessment of serum endocan levels in children with juvenile idiopathic arthritis. *Arch Rheumatol*. 2017;33:168-173.
- Van Oosten BW, Barkhof F, Scholten PE, et al. Increased production of tumor necrosis factor alpha, and not of interferon gamma, preceding disease activity in patients with multiple sclerosis. *Arch Neurol*. 1998;55:793-798.

24. Yoon KH, Kim SY, Moon YS, Roh D, Lee SK, Kim DH. The relationship between serum endocan levels and depression in Alzheimer's disease. *Dis Markers*. 2016;2016:8254675.
25. Kealy J, Greene C, Campbell M. Blood-brain barrier regulation in psychiatric disorders. *Neurosci Lett*. 2020;726:133664.
26. Akil E, Alp R, Aluclu MU, Acar A, Kaplan I. Serum endocan levels in multiple sclerosis relapse and remission. *Eur Rev Med Pharmacol Sci*. 2021;25(11):4091-4098.
27. Atalar AC, Köseoğlu M, Yavuz N, Erdal Y, Oğuz O, Emre U. Could serum endocan be a vascular endothelial marker in relapsing-remitting multiple sclerosis? *Turk J Neurol*. 2021;27:257-262.
28. Nakamura T, Mizuno S. The discovery of hepatocyte growth factor (HGF) and its significance for cell biology, life sciences and clinical medicine. *Proc Jpn Acad Ser B Phys Biol Sci*. 2010;86:588-610.
29. Maina F, Klein R. Hepatocyte growth factor, a versatile signal for developing neurons. *Nat Neurosci*. 1999;2:213-217.
30. Benkhoucha M, Santiago-Raber ML, Schneider G, et al. Hepatocyte growth factor inhibits CNS autoimmunity by inducing tolerogenic dendritic cells and CD25+Foxp3+ regulatory T cells. *Proc Natl Acad Sci U S A*. 2010;107:6424-6429.
31. Lalive PH, Paglinawan R, Biollaz G, et al. TGF-beta-treated microglia induce oligodendrocyte precursor cell chemotaxis through the HGF-c-Met pathway. *Eur J Immunol*. 2005;35:727-737.
32. Kitamura K, Iwanami A, Nakamura M, et al. Hepatocyte growth factor promotes endogenous repair and functional recovery after spinal cord injury. *J Neurosci Res*. 2007;85:2332-2342.
33. Rocha SF, Schiller M, Jing D, et al. Esm1 modulates endothelial tip cell behavior and vascular permeability by enhancing VEGF bioavailability. *Circ Res*. 2014;115:581-590.
34. Zhang X, Zhuang R, Wu H, et al. A novel role of endocan in alleviating LPS-induced acute lung injury. *Life Sci*. 2018;202:89-97.
35. Bécharde D, Gentina T, Delehedde M, et al. Endocan is a novel chondroitin sulfate/dermatan sulfate proteoglycan that promotes hepatocyte growth factor/scatter factor mitogenic activity. *J Biol Chem*. 2001;276(51):48341-48349.
36. Delehedde M, Devenyns L, Maurage CA, et al. Endocan in cancers: a lesson from a circulating dermatan sulfate proteoglycan. *Int J Cell Biol*. 2013;2013:705027.
37. Kul A, Ateş O, Melikoğlu MA, et al. Endocan measurement for active Behçet disease. *Arch Rheumatol*. 2017;32:197-202.
38. Iacobaeus E, Amoudruz P, Ström M, et al. The expression of VEGF-A is down regulated in peripheral blood mononuclear cells of patients with secondary progressive multiple sclerosis. *PLoS One*. 2011;6:e19138.
39. Ruiz de Almodovar C, Lambrechts D, Mazzone M, et al. Role and therapeutic potential of VEGF in the nervous system. *Physiol Rev*. 2009;89:607-648.
40. Nikolenko VN, Oganessian MV, Vovkogon AD, et al. Current understanding of central nervous system drainage systems: implications in the context of neurodegenerative diseases. *Curr Neuropharmacol*. 2020;18:1054-1063.