

Can CRP/melatonin ratio measurement be used as a predictor of multiple sclerosis?

¹Gholamreza Asadikaram, ¹Hossein Ali Ebrahimi Meimand, ^{2,3}Mohammad Kazemi Arababadi, ^{2,4}Mahmood Sheikh Fathollahi, ⁵Saam Noroozi

¹Neurology Research Center and Department of Biochemistry, School of Medicine, Kerman University of Medical Sciences, Kerman; ²Immunology of Infectious Diseases Research Center, Research Institute of Basic Medical Sciences, ³Department of Laboratory Sciences, Faculty of Paramedicine, ⁴Department of Epidemiology and Biostatistics, Faculty of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan; ⁵Student Research Center, Kerman University of Medical Sciences, Kerman, Iran.

Abstract

Background & Objective: This study aimed to find a biomarker to predict the development of multiple sclerosis (MS). Serum levels of vitamin D3, C-reactive protein (CRP) and melatonin and their ratio were evaluated to find the valuable cut-off point. **Methods:** Serum levels of vitamin D3, CRP and melatonin were evaluated using commercial ELISA kit in newly diagnosed MS patients and compared with healthy controls. **Results:** Serum CRP level significantly increased and serum melatonin level significantly decreased in MS patients in comparison to controls. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy for the cut-off point of CRP/melatonin ratio ≥ 78.29087 were 80%.

Conclusion: CRP/melatonin ratio ≥ 78.29087 may be used for prediction of MS in an at risk population.

Keywords: CRP, melatonin, multiple sclerosis, vitamin D3

INTRODUCTION

Melatonin has immune-regulatory effects. In addition, it shows anti-oxidative properties that allow *scavenging of oxidative stress* in the inflamed tissues.¹ Accordingly, there are several investigations which showed decreased melatonin levels in MS patients.¹ On the other hand, C-reactive protein (CRP) is an acute-phase reactant whose level rises when there is inflammation throughout the body.² It has been demonstrated that serum levels of CRP increased significantly in multiple sclerosis (MS), as an aseptic autoimmune diseases process.³ CRP/melatonin ratio may also be useful predictor of MS. Additionally, it has been reported that vitamin D3 is an immunomodulator and its serum level is significantly associated with immune system functions.⁴ Therefore, the aim of this study was to evaluate serum levels of vitamin D3, CRP and melatonin and also CRP/melatonin ratio in an MS population in comparison to healthy controls to determine the value of the ratio for prediction of MS.

METHODS

In this cross-sectional study, 45 newly diagnosed MS patients consisting of 30 females and 15 males and 45 age and sex matched healthy controls were recruited. The patients had a relapse of MS 2 to 4 weeks before diagnosis of MS; they were considered as new cases of MS. The diagnosis of MS was based on the McDonald criteria.⁵ As the patients were newly diagnosed cases, they were not under treatment with any drugs.

All participants signed the informed consent (Ethic committee serial no: k/93/166). All the study subjects were non-smoker and did not suffer from other inflammatory disease or infectious disease.

Intravenous blood was collected immediately after diagnosis of MS, and before alteration in physical activity and sunlight exposure. The 25-OH-Vitamin D3, CRP and melatonin levels were measured using ELISA kits (Diagnostics Biochem, Canada).

Continuous variables were compared using independent two-sample *t* test. Receiver Operating

Address correspondence to: Mohammad Kazemi Arababadi, Immunology of Infectious Diseases Research Center, Research Institute of Basic Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran. Tel: +98 9132926113, Email: dr.kazemi@rums.ac.ir; Saam Noroozi: Department of Clinical Biochemistry, School of Medicine, Fasa University of Medical Sciences, Fasa, Iran. Tel: +98 9131406916, email: saam.noroozi@gmail.com, Gh_asadi@kmu.ac.ir

Characteristic (ROC) curve analysis was used to determine optimal cut-off points for MS detection.

RESULTS

There was no significant alteration of the serum levels of vitamin D3 ($p= 0.323$) in the MS patients (20.20 ± 1.50 ng/mL) when compared to the healthy controls (22.81 ± 2.14 ng/mL). On the other hand, the serum CRP level was significantly elevated ($p< 0.001$) and melatonin level significantly decreased ($p< 0.001$) in the MS patients as compared to the healthy controls (Figure 1).

Sensitivity, specificity, positive predictive value, negative predictive value and accuracy for the cut-off point of CRP/melatonin ≥ 78.29087 (for total MS patients) and CRP/melatonin ≥ 87.77778 (for female MS patients) were 80%, while the corresponding values for the cut-off point of CRP/melatonin ≥ 65.79257 for male MS patients were 80%, 86.7%, 85.7%, 81.3% and 83.3%, respectively (Table 1).

DISCUSSION

Based on the results, we hypothesized that the CRP/melatonin ratio can lead to a valuable cut-off point to separate between MS patients and healthy controls. CRP/melatonin ≥ 78.29087 is a suitable cut-off point to separate MS patients from the healthy controls with an 80% sensitivity and specificity.

Serum levels of melatonin are elevated in other pro-inflammatory diseases including neonatal sepsis and ankylosing spondylitis.⁶ Interestingly, melatonin has a positive relation with CRP in these disorders.⁶ Additionally, topical administration of melatonin leads to decreased levels of CRP.⁷ Therefore, it seems that expression of melatonin is different depending on the particular disorder. Accordingly, increased serum levels of melatonin may be associated with MS and CRP/melatonin ratio may be considered as a suitable screening marker for prediction of MS.

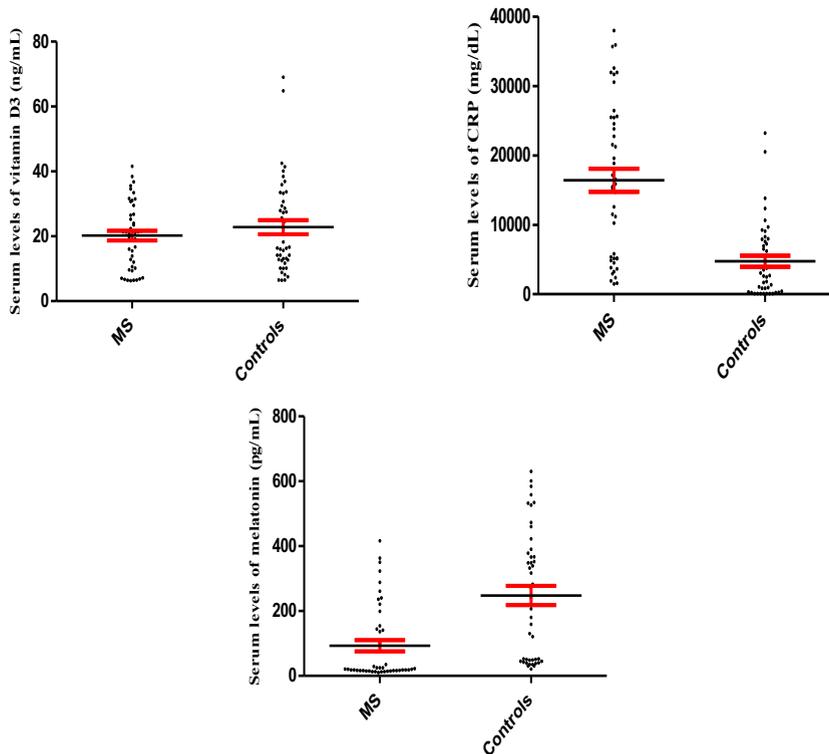


Figure 1. Serum levels of vitamin D3, CRP and melatonin in MS patients in comparison to healthy controls. The figure illustrates that serum levels of CRP and melatonin significantly increased and decreased, respectively, in MS patients compared to healthy controls, while serum levels of vitamin D3 did not differ across the two groups.

Table 1: The calculated cut-off points for CRP/melatonin ratio in prediction of MS

Total	Males	Females
CRP/Melatonin \leq 78.29087	CRP/Melatonin \leq 65.79257	CRP/Melatonin \leq 87.77778
Sen. = 80%	Sen. = 80%	Sen. = 80%
Spe. = 80%	Spe. = 86.7%	Spe. = 80%
PV ⁺ = 80%	PV ⁺ = 85.7%	PV ⁺ = 80%
PV ⁻ = 80%	PV ⁻ = 81.3%	PV ⁻ = 80%
Acu. = 80%	Acu. = 83.3%	Acu. = 80%
LR ⁺ = 4.0000	LR ⁺ = 6.0000	LR ⁺ = 4.0000
LR ⁻ = 0.2500	LR ⁻ = 0.2308	LR ⁻ = 0.2500
AUC = 0.8790	AUC = 0.9111	AUC = 0.8711

Table illustrates that CRP/Melatonin \geq 78.29087, \geq 65.79257 and \geq 87.77778 may be the best cut-off points for prediction of MS in both genders, males and females, respectively, as a screening test.

CRP; C-reactive Protein, MS; Multiple Sclerosis, Sen.; Sensitivity, Spe.; Specificity, PV⁺; Positive Predictive Value, PV⁻; Negative Predictive Value, Acu.; Accuracy, LR⁺; Positive Likelihood Ratio, LR⁻; Negative Likelihood Ratio, AUC; Area Under the ROC (Receiver Operating Characteristic) Curve.

Interpretation of cut-off points for CRP/Melatonin in both genders (total)

Sen. = 80% means in 80% of MS patients, CRP/Melatonin was more than or equal to 78.29087.

Spe. = 80% means in 80% of healthy controls patients, CRP/Melatonin was less than 78.29087.

PV⁺ = 80% means 80% of individuals with CRP/Melatonin more than or equal to 78.29087, were MS.

PV⁻ = 80% means 80% of individuals with CRP/Melatonin less than 78.29087, were healthy controls.

Acu. = 80% means in 80% of studied population, the cut-off point of 78.29087 could correctly distinct MS and healthy controls.

LR⁺ = 4.0000 means MS patients were 4 times more likely to have CRP/Melatonin more than or equal to 78.29087 compared to healthy controls.

LR⁻ = 0.2500 means MS patients were 0.25 times more likely to have CRP/Melatonin less than 78.29087 compared to healthy controls.

AUC value means how good the presented cut-off point could discriminate MS and healthy controls. AUC value near to 1.000 means the presented cut-off point could exactly discriminate MS and healthy controls.

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