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# Adiponectin as a novel predictive biomarker of multiple sclerosis course

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**ABSTRACT**

Multiple sclerosis (MS) is a serious neurological disease, the actual worldwide prevalence of which is estimated to be 2,8 million people (35,9 per 100,000). During the course of MS, various neurological symptoms and its complications result in raising patient disability, which range from skeletal muscles impairment, to losses in cognitive functions. Achieving control over course of MS progression appears to be crucial in its treatment. This enforces the need for recognizing novel predictive factors so as to allow prognosis of future remissions and/or progressions. Adiponectin, hormone secreted by adipose tissue, currently is considered as a possible candidate for such a biomarker. The aim of this review is to summarise present knowledge and to assess possible clinical usage. According to collected data, adiponectin measurements in serum and cerebrospinal fluid appear to provide plausible and useful biomarkers in predicting the course of MS. Further studies are, however, needed, especially using non-invasive, but promising sources such as saliva.

## INTRODUCTION

Multiple sclerosis (MS) is a serious neurological disease of which the actual worldwide prevalence is estimated to be 2,8 million people (35,9 per 100,000). From 2013 to 2020, its occurrence increased in every world region. The mean age of MS diagnosis is 32 years, and females are twice as likely to suffer to MS than males [1]. MS occurs as four main clinical types that determine its course: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PRMS) and secondary progressive MS (SPMS). MS is the most common immune-related disease affecting the central nervous system (CNR).

During the course of MS, various neurological symptoms and complications result in patient disability. These range from skeletal muscles impairment, to losses in cognitive functions [2]. In 2013, MS was a cause of death to 19,8 thousand people worldwide [3].

Due to MS complications, seriousness and growing prevalence, much attention is paid by the scientific world to understanding the aetiopathogenesis and the molecular background of its course. However, the presently mostly-accepted notion is to describe MS as a neurological autoimmune disease, and to group it with myasthenia gravis and Guillain-Barré syndrome. The impact of contagious, environmental or hormonal factors on its onset is still considered.

Achieving control over the course of MS progression appears to be crucial in its treatment. This enforces the need to recognize novel predictive factors, hence allowing the prognosis of future remissions and/or progressions. Adiponectin, hormone secreted by the adipose tissue, is currently considered a possible candidate for such a biomarker. The aid of this review is to summarise present knowledge and to assess its possible clinical usage.

## ADIPONECTIN-RELATED IMMUNOMODULATION

Adiponectin is one of the adipokines. These are hormones produced by the adipose tissue. Adiponectin has three different molecular weights: low-molecular weight (LMW) (trimer), middle-molecular weight (MMW) (hexamer) and high-molecular weight (HMW) (multimer), as well as two main receptors: AdipoR1 and AdipoR2 [4]. Although adiponectin secretion takes place only in the adipose tissue, its level in obesity is significantly lower. This is called the "adiponectin paradox" and probably is brought about by higher levels of glycosyl phosphatidylinositol-phospholipase D (GPI-PLD), which inhibits adiponectin secretion [5]. Adiponectin degradation in renal apparat is suspected,

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according to its high level in chronic kidney disease, with its normalisation after successfully accepted kidney transplant [6,7].

Although adiponectin is mainly involved in metabolic regulation through increasing tissue insulin-sensibility [8], this hormone also has antitumour activity and affects the downregulation of various growth factors. Moreover, crucial to MS development, it participates in immune response modulation [9].

Adiponectin-level changes were reported in numerous immune-related diseases, including inflammatory diseases such as inflammatory bowel disease [10], and autoimmune diseases like systemic lupus erythematosus [11], Graves' disease [12] and Sjogren disease [13]. In type 1 diabetes [14] and in autoimmune myocarditis, the level of adiponectin has not been found to significantly change [15].

Numerous mechanisms of adiponectin impact on immune system cells are described in scientific literature. Adiponectin addiction to isolated T-cell cell lines results in pro-inflammatory cytokines secretion (IFNγ, IL-6) and enhanced differentiation to the Th1 subpopulation, whereas macrophage activity has been indicated by means of pro-inflammatory activation via classical (M1) approaches [16]. Adiponectin also displays complement system activation via classical manner through C1q binding, which has common domain [17,18]. In addition, adiponectin shares common domain with tumour necrosis factor [18].

In contrast, hypoadiponectinemia in atherosclerosis results with increased CRP-secretion in endothelial cells – this is seen as a hormonal cardiovascular protective effect [19]. Also, in experimental models of autoimmune encephalitis, adiponectin-related receptor AdipoR2-tranduced pathway activity resulted in suppression of Th17 differentiation [20]. What is more, a high-dose steroid therapy in thyroid orbitopathy resulted in significant lowering of adiponectin levels, whereas in both groups (before and after therapy), its level was still significantly higher in comparison to a healthy control group [12].

## METABOLIC DISORDERS RELATION TO MULTIPLE SCLEROSIS

There are limited data regarding glucose metabolism dysregulation in MS. In one study, research consisting of 19 newly diagnosed patients and 19 healthy donors showed no significant change in fasting glycemia, but research group members had significantly worse reaction in oral glucose toleration testing, suggesting the role of insulin-resistance with hyperinsulinemia in MS aetiopathogenesis [21]. Moreover, Mendelian randomisation studies have recognized a positive correlation between obesity (especially in childhood) and multiple sclerosis risk. Adiponectin impact on this linking was, however, rejected in secondary studies [22,23]. adiponectin's impact on this linking was refused in secondary studies[24,25].

In a further study, aerobic interval training undertaken by 40 women with MS (EDSS≤3) established the positive effect of exercises on their immune and hormonal systems, including significant elevation of adiponectin levels [26]. In contrast, similar research (but performed on smaller research group; n=30) showed no significant change in adiponectin levels after exercises (but showed so in different biomarker levels) [27].

## ADIPONECTIN-RELATED GENES POLYMORPHISM IN MS

A genetical research performed on 305 MS patients and 255 healthy individuals confirmed that rs1501299TT genotype and rs1501299T allele (responsible for adiponectin production) were significantly higher in male controls compared to male patients, but without any significant difference with no gender categorisation. Additionally, rs1501299TT genotype was associated with susceptibility to PPMS [28].

## ADIPONECTIN LEVEL IN SERUM

The previously cited research, which suggested insulin-resistance with hyperinsulinemia in MS aetiopathogenesis, did not reveal significant difference in lactate, GLP-1, total, HDL and LDL cholesterol, triglycerides, interleukin 6, tumour necrosis factor, C-reactive protein, resistin, leptin, adiponectin levels between research (n=19) and newly-diagnosed MS) and control (n=19; healthy) groups [21]. In a MS mice model, however, genetically determined lack of adiponectin resulted in stronger pro-inflammatory reaction. Here, lymphocytes proliferated more intensively, and secreted more pro-inflammatory cytokines (IFN-γ, IL-17, TNF-α, IL-6). Administration of adiponectin then increased the percentage of Treg cells, suppressing inflammatory reaction [29]. The research, which consisted of 40 healthy subjects and 50 MS patients (24 with classical course and 26 with benign), showed that adiponectin and MCP-1 might be considered as a prognostic factors of severe MS course, according to their statistically significant correlation with disease course seriousness [30].

In another study, data collected from blood samples of 99 MS patients and 89 healthy subjects let researchers confirm higher levels of adiponectin among MS patients, in comparison to a healthy control group. The follow-up (3.6±2.20 years) led the same researchers to confirm the prognostic value of adipokine, because patients with higher levels achieved worse Expanded Disability Status Scores [31].

A Turkish research group compared adipokine serum levels in patients with MR wherein the first clinical manifestation of their illness was optic neuritis (n=24) (which is correlated with RRMS), to those with different MR clinical picture (n=31) and healthy donors (n=40). They demonstrated significantly higher levels of adiponectin, depending on both MS occurrence and its severity (defined as above) [32].

The negative correlation between adiponectin level and MS relapse hazard was also confirmed in a study performed on a paediatric populace (research group n=32; control group n=67). The adiponectin level was significantly lower in MS patients, in comparison to healthy donors [33]. In contrast, a 2-year-long randomised controlled trial performed on 88 MS patients showed no significant difference in adiponectin level depending on disease severity or treatment response [34].

In a further study, the difference in adiponectin levels among patients with different MS type (n=80) was denied. The only established difference was significantly higher level of adiponectin in female MS patients, in comparison to males [35].

Research conducted by a Polish research group also showed no significant difference in adiponectin level among 31 MS patients in comparison to 27 healthy individuals. The report's authors stated, however, that their data refused adiponectin as a biomarker only at the initial phase of MS, giving attention to plausible involvement of adiponectin in the course of MS progression [36].

A research group from Brazil, using machine learning, has developed a diagnostic algorithm that depends on four biochemical serum parameters: zinc, adiponectin, total radical-trapping antioxidant parameter (TRAP) and sulfhydryl (SH) groups. Basing on those biomarkers, the algorithm is able to diagnose multiple sclerosis with 92,9% accuracy and 90,6% validation [37].

## ADIPONECTIN LEVEL IN CEREBROSPINAL FLUID

Research conducted on 66 MS patients and 24 age- and sex-matched controls confirmed that adiponectin level in cerebrospinal fluid (CSF) correlates with CSF IgG level, and that CSF/serum albumin ratio directly correlated with CSF/serum adiponectin ratio. The achieved data also demonstrated that higher concentration of adiponectin in CSF might be considered as a worse prognostic factor, because in the progressive form, in comparison to remission-remitting form, the level of adipokine was significantly higher. In addition, patients with higher adipokine level had worse scores in MS severity tests (EDSS) after a 4,5-year follow-up [38].

## ADIPONECTIN LEVEL IN SALIVA

Starting in 2012, the possibility of adiponectin level measurements from salivary samples has come into existence [39], and their usage in metabolic disorders is now widely considered [40,41]. Unfortunately, in according to available literature, its significance in MS diagnosis has not been fully researched. The mentioned studies, however, confirm correlation between salivary and serum levels of adiponectin [42]. The non-invasiveness of this biomarker may be very useful and applied to telemedical systems that are projected currently for other diseases [43].

## CONCLUSIONS

According to collected data, adiponectin measurements in serum and cerebrospinal fluid appear to be plausible and useful biomarkers in predicting the course of MS. Further studies are needed, especially using non-invasive but promising sources such as saliva.

## CONFLICT OF INTERESTS

None

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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