

# The Effect of Methylprednisolone, Interferon Beta and Glatiramer Acetate Treatment on the Levels of Leptin, Adiponectin and Resistin in Multiple Sclerosis Patients

Slawomir Michalak<sup>1,2\*</sup>, Lukasz Jernas<sup>3\*</sup>, Ewa Wysocka<sup>4</sup>, Krystyna Osztynowicz<sup>1</sup>, Elzbieta Tokarz-Kupczyk<sup>3</sup>, Halina Wygladalska-Jernas<sup>3</sup> and Wojciech Kozubski<sup>3</sup>

<sup>1</sup>Department of Neurochemistry and Neuropathology, Poznan University of Medical Sciences, 60-355 Poznan, Przybyszewskiego str. 49, Poland

<sup>2</sup>Neuroimmunological Unit, Polish Academy of Sciences, 60-355 Poznan, Przybyszewskiego str. 49, Poland

<sup>3</sup>Department of Neurology, Poznan University of Medical Sciences, 60-355 Poznan, Przybyszewskiego str. 49, Poland

<sup>4</sup>Department of Clinical Biochemistry and Laboratory Medicine, Chair of Chemistry and Clinical Biochemistry, Poznan University of Medical Sciences, Poland

## Abstract

**Objective:** Adipocytokines are cytokine-like mediators that link adipose tissue function with inflammatory and autoimmune processes, and have a suggested role in the pathogenesis of multiple sclerosis (MS). The aim of this study was to analyze the effects of methylprednisolone, interferon-1b (INF) and glatiramer acetate (GA) on leptin, resistin, and adiponectin concentrations in relapsing-remitting MS (RRMS) patients.

**Methods:** The study included 154 RRMS patients who were hospitalized in the Department of Neurology, Poznan University of Medical Sciences. The comparison group included 31 patients with myasthenia gravis (MG) and 39 healthy controls. Serum levels of leptin, adiponectin, and resistin were evaluated before treatment initiation. In the RRMS patients treated with methylprednisolone, adipocytokine evaluation was performed one day after the therapy. Patients treated with INF or GA were evaluated at 1 month and 6 months. Routine neurological examination and expanded disability status scale (EDSS) scoring were performed, and MRI scans were analyzed for the localization of demyelinating plaques. Body mass index, glycemia, and insulin levels were evaluated and homeostatic model assessment insulin resistance index (HOMA-IR) was calculated.

**Results:** Adiponectin and resistin levels in RRMS and MG patients were increased compared to controls, but adiponectin levels were lower in RRMS than MG patients. Intravenous methylprednisolone in RRMS with relapse caused an elevation of leptin concentration. INF treatment caused a significant, time-dependent effect on resistin concentration. GA administration influenced only resistin concentration as a long-term effect. No relationship between adipocytokines and metabolic status or insulin resistance was found.

**Conclusions:** We identified resistin as the most important adipocytokine associated with RRMS. Its concentrations are reduced by first line immunomodulatory treatment, which produces a milieu of beneficial inflammatory and metabolic processes. On the other hand, the routine treatment of MS relapses with methylprednisolone induces harmful metabolic and inflammatory effects that may be mediated by elevated leptin levels.

**Keywords:** Leptin; Resistin; Adiponectin; Multiple sclerosis; Methylprednisolone; Interferon-1b; Glatiramer acetate

## Introduction

Adipocytokines are cytokine-like mediators produced by adipose tissue and are involved in inflammation, immune response, and metabolism. Leptin, adiponectin, and resistin belong to the most abundant family of adipocytokines that link adipose tissue function with inflammatory and autoimmune processes [1]. Leptin is recognized as an immunendocrine mediator. On the one hand, it controls the homeostatic balance between food intake and energy expenditure, its concentration increases during fat accumulation and decreases during fasting. The concentration of leptin in the sera of obese individuals is increased, indicating these individuals have leptin-resistance [2]. Additionally, its reduction contributes to insulin resistance in animal models [3]. On the other hand, leptin acts as a pro-inflammatory adipocytokine by stimulating the production of interleukin 6 (IL-6), tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin 12 (IL-12) in monocytes and macrophages [4], and inhibiting the production of anti-inflammatory cytokines, including interleukin 4 (IL-4), in CD4+ T cells [5]. Resistin is also a pro-inflammatory adipocytokine that is produced by adipocytes, macrophages, and mononuclear cells. It stimulates the production of pro-inflammatory cytokines like TNF- $\alpha$  and IL-12 [6]. Moreover, resistin regulates the immune response by influencing

regulatory T cells. It inhibits the expression of interferon regulatory factor (IRF)-1 and related cytokines, IL-6, interleukin 23p19 (IL-23p19) and interleukin 12p40 (IL-12p40) in dendritic cells, which also mediate the upregulation of Forkhead box P3 (FoxP3) expression in CD4+ T by resistin [7]. The decreased insulin-mediated downregulation of gluconeogenesis and increased glycogenolysis [8] and decrease in insulin-stimulated phosphorylation of key regulatory liver enzymes, all metabolic effects caused by resistin [9], leads to hepatic insulin resistance. In contrast to leptin and resistin, adiponectin acts as an anti-inflammatory adipocytokine [1], and also promotes insulin sensitivity

**\*Corresponding author:** Slawomir Michalak, Department of Neurochemistry and Neuropathology, Poznan University of Medical Sciences, 60-355 Poznan, Przybyszewskiego str. 49, Poland, Tel: +48 61 8691 443; Fax: +48 61 8691 444; E-mail: [swami622@gmail.com](mailto:swami622@gmail.com)

**Received** December 21, 2013; **Accepted** February 19, 2014; **Published** February 27, 2014

**Citation:** Michalak S, Jernas L, Wysocka E, Osztynowicz K, Kupczyk ET, et al. (2014) The Effect of Methylprednisolone, Interferon Beta and Glatiramer Acetate Treatment on the Levels of Leptin, Adiponectin and Resistin in Multiple Sclerosis Patients. J Neurol Neurophysiol S12: 005. doi:10.4172/2155-9562.S12-005

**Copyright:** © 2014 Michalak S, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

in skeletal muscles, in the liver and adipose tissue [10]. However, it has also been shown to increase the production of interleukin 8 (IL-8) in human macrophages stimulated by lipopolysaccharides [11].

The observation that adipocytokines are involved in inflammatory and immune processes has led to increased interest over the last few years regarding their role in multiple sclerosis (MS). Leptin has been suggested as a link between immune tolerance, metabolic state and autoimmunity. It is involved in the development of experimental autoimmune encephalomyelitis (EAE) [12,13] and the elimination or neutralization of leptin limits an autoimmune response in the course of EAE by reducing delayed-type hypersensitivity against proteolipid protein, CD4<sup>+</sup> T cell hyporesponsiveness against myelin antigens, and increasing IL-4 and IL-10 production and the number of regulatory FoxP3 CD4<sup>+</sup>T cells [14].

Elevated resistin concentrations were found in patients with relapsing-remitting multiple sclerosis (RRMS) compared to healthy controls [15]. Moreover resistin and TNF- $\alpha$  concentrations were higher in patients monozygous for GG with the "rs1862513" genotype who had multiple sclerosis [16]. Thus, resistin gene polymorphisms contribute to an increased risk for MS.

Adiponectin concentrations in cerebrospinal fluid were increased in MS individuals compared to their non-MS twins and did not correlate with plasma concentrations, suggesting intrathecal production [17]. Reports on serum adiponectin concentration in MS patients compared to controls have demonstrated equivocal results. A lowering in adiponectin concentration was observed in MS patients [15]. However, recently, an elevated adiponectin concentration was reported in the context of increased risk for cardiovascular diseases in MS patients, and a negative correlation between small HDL-c and adiponectin concentration was found [18].

Limited data exist on the effect of immunomodulatory treatment on adipocytokines levels in MS patients [19,20].

The aim of our study was to analyze the effect that the routine treatment of relapse with methylprednisolone and first line immunomodulatory drugs (interferon-1b and glatiramer acetate) has on the leptin, resistin and adiponectin concentrations in RRMS patients. We undertook an analysis of the relationship between insulin resistance and the concentration of adipocytokines in RRMS patients. The inclusion of myasthenia gravis patients in addition to healthy controls was justified by the need to compare the effects another autoimmune disorder has on the adipocytokine profile.

## Materials and Methods

The study included 154 patients with relapsing-remitting multiple sclerosis (RRMS) hospitalized in the Department of Neurology at Poznan University of Medical Sciences, Poland and patients participating in an immunomodulatory treatment program being carried out for 2 years by the National Health Fund. Among RRMS patients, 31 were treatment naïve, 52 who had a relapse were treated with standard [21] intravenous methylprednisolone (1.0 g i.v. for 5 days), 55 underwent interferon beta-1b (250  $\mu$ g subcutaneously every other day) and 16 glatiramer acetate (subcutaneously 20 mg / day) treatment, respectively. In the RRMS group, 15 patients (9.7%) had associated diabetes.

The comparison group consisted 31 myasthenic patients (11 who had diabetes [35%], 2 who had RRMS) included into the study before initiation of any treatment.

**Exclusion criteria were:** diagnosis of autoimmune disorders (e.g. lupus and other connective tissue disorders, acute disseminated encephalomyelitis, neuromyelitis optica, Hashimoto thyroiditis, celiac disease, gastrointestinal autoimmune diseases), sarcoidosis, central nervous system infections or current administration, or history, of immunosuppression.

The control group consisted of 39 age matched healthy volunteers not exposed to any treatment.

The levels of leptin, adiponectin, and resistin were evaluated in all participants of the study before the initiation of treatment by means of an ELISA (DRG Medtek, USA). In RRMS patients with relapse who were treated with methylprednisolone, the second adipocytokine evaluation was performed one day after the therapy. In patients treated with interferon-1b or glatiramer acetate the time points for adipocytokine evaluation were after 1 month and 6 months of the treatment. Routine neurological examination and EDSS scoring were performed in all RRMS patients at the baseline. Neurological examination and EDSS score were next repeated at the 1st and 6th month of the treatment and during relapse.

Magnetic resonance imaging (MRI) scans were analyzed for the localization of demyelinating plaques (supratentorial, infratentorial, spinal cord).

The metabolic aspects analyzed in all participants included the following: body mass index (BMI), glycemia, insulin levels (by means of ELISA, BioSource), and insulin resistance index HOMA calculated by the following formula:

$$\text{HOMA-IR (insulin-resistance) index} = [\text{insulin } (\mu\text{U/ml}) \times \text{glycemia (mg/dl)}] / 405.$$

Statistical analysis was performed with the use of a licensed version of MedCalc 12.7.5.0 (64 bit) software. First, the distribution of results was analyzed with the D'Agostino-Pearson test. The variables that had a normal distribution were expressed as mean  $\pm$  SD and tested with an F test; the variables that had a non-Gaussian distribution were expressed as median and interquartile range and analyzed with the Mann-Whitney test. Dependent variables represented by the levels of adipocytokines during treatment with methylprednisolone, interferon-1b and glatiramer acetate were compared with the Kruskal-Wallis test.

The study protocol was accepted by the Ethics Committee of Poznan University of Medical Sciences and each participant recruited gave informed consent.

## Results

We did not find any significant differences in age, BMI, glycemia, or insulin levels between RRMS patients, myasthenia gravis patients, and controls (Table 1).

Adiponectin and resistin levels in RRMS and myasthenia gravis patients were increased compared to controls (Table 1); moreover, in RRMS patients, adiponectin levels were lower than in those with myasthenia gravis (Table 1). Resistin concentration correlated positively with the duration of RRMS ( $r=0.186$ ;  $P=0.0456$ ). There were no differences ( $P>0.05$ ) in leptin, adiponectin, or resistin concentrations between non-diabetic and diabetic RRMS patients (Table 2).

Insulin resistance represented by HOMA-IR was found only in diabetic RRMS patients (Figure 1). There were no differences in HOMA-IR between RRMS, MG patients, and controls, nor between non-diabetic and diabetic RRMS and MG patients (Table 1).

	Controls [C] n=39	Myasthenia gravis patients [MG] n=28	RRMS patients n=123
Age	38.9 ± 7.0	34 ± 19	42 ± 12
BMI	22 ± 3	22 ± 5	23 ± 4
Glucose	86 ± 17	113 ± 30	104 ± 20
Insulin [mIU/l]	11.26 6.55-26.20	7.58 3.6-23.0	18.23 3.02-73.23
HOMA-IR	2.39 ± 0.69	2.11 ± 0.98	4.68 ± 1.73
Leptin [ng/ml]	11.76 4.89-22.40	13.73 7.31-25.38	12.70 5.98-24.64
Adiponectin [ng/ml]	4.65 3.50-5.50	2 197.20 * 1 795.12-3 042.08	1 489.29 ** 7.36-28.69
Resistin [ng/ml]	4.895 2.61-5.92	17.01 † 10.52-28.14	21.94 ‡ 10.22-29.93

\*P=0.0386 RRMS vs. MG; \*\*P=0.0064 RRMS vs. C; †P=0.0002 MG vs. C; ‡P=0.0002 RRMS vs. C; §P=0.0010 MG vs. C.

**Table 1:** Demographic and metabolic data and adipocytokine concentrations in the studied groups of patients.

	Leptin [ng/ml]	Adiponectin [ng/ml]	Resistin [ng/ml]
Non diabetic RRMS N=139	9.07 3.61-15.84	770.76 4.60-2608.42	9.75 7.43-13.38
Diabetic RRMS N=15	11.57 3.54-16.89	793.24 4.32-1480.60	8.60 4.85-11.44
Non-diabetic MG N=20	3.98 3.18-9.02	2219.30 1486.96-3142.88	8.96 5.63-15.25
Diabetic MG N=11	3.55 3.07-5.20	2261.94 162.87-2422.69	7.08 4.88-9.01

**Table 2:** Adipocytokine concentrations in non-diabetic and diabetic RRMS and MG patients (P>0.05).

Intravenous methylprednisolone in RRMS with relapse caused an increase (P=0.001) in leptin concentration (14.10; 6.38-20.14 vs. 6.95; 3.21 to 14.39 ng/mL; median, interquartile range) and had no effect on adiponectin (8.21; 4.16-2700.88 vs. 944.69; 5.11-2523.85 ng/mL, P=0.6674) and resistin concentration (10.03; 8.16-14.76 vs. 9.42; 6.89-12.92 ng/mL, P=0.1498). Resistin concentration correlated positively with HOMA-IR insulin resistance index (Spearman's  $r=0.351$ , P=0.0386) in methylprednisolone treated patients.

Interferon-1b treatment caused a significant (P<0.0001) time-dependent effect on resistin concentration and did not modify leptin

(P=0.9633) or adiponectin (P=0.3338) concentrations (Table 3). There was no relation between EDSS score and adipocytokines concentrations in interferon 1b treated patients during the 6 months of observation.

Glatiramer acetate treatment influenced only resistin concentration after 6 months, and showed no effect on either adiponectin (P=0.9911) or leptin (P=0.5951) concentrations (Table 4). In the glatiramer acetate group at baseline we observed differences (P=0.0256) in resistin concentration between patients who received an EDSS score of 0 (57.58; 48.86-79.11 ng/mL, median interquartile range), 1 (32.52; 28.60-36.02 ng/mL) and 1.5 (66.58; 54.2-123.70 ng/mL). Further on during the treatment there was no relationship between EDSS score and adipocytokines concentration.

We did not observe a correlation between adipocytokine concentrations and the number of relapses during interferon-1b and glatiramer acetate treatment, or before the treatment initiation. Moreover, we did not find any relationship between the localization of demyelinating plaques (supratentorial, infratentorial, spinal cord) in MRI scans and the concentration of adipocytokines.

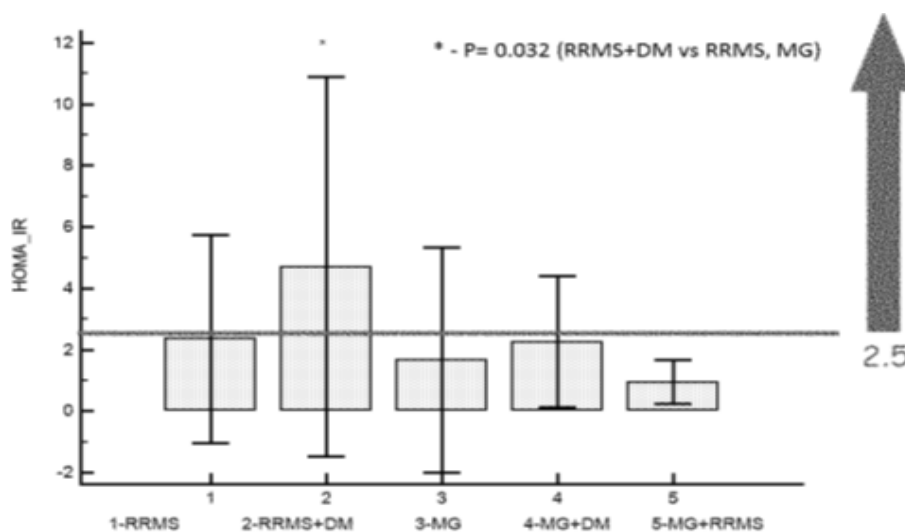
Adipocytokine concentrations did not correlate with the HOMA-IR insulin resistance index in interferon-1b and glatiramer acetate treated patients.

## Discussion

In our study we found that neurological autoimmune disorders are associated with increased concentrations of adipocytokines with a particular significance for resistin in RRMS patients. Routine methylprednisolone treatment induced a harmful effect that led to an increase in leptin levels. First line immunomodulatory treatment by reducing resistin concentration limits the immune response mediated by adipocytokines in RRMS patients.

In the age, BMI, and insulin resistance balanced groups that were involved in our study, we observed increased concentrations of resistin and adiponectin in RRMS and MG patients.

To the best of our knowledge, this is the first study on adipocytokines in RRMS that considers the metabolic and insulin resistance status of the analyzed subjects. Thus, we may suggest that the observed changes in



**Figure 1:** Insulin resistance index HOMA-IR in studied subgroups of patients.

	EDSS [median; minimum-maximum]	Leptin [ng/ml]	Adiponectin [ng/ml]	Resistin [ng/ml]
INF 1b baseline	1.0 0-2.5	14.61 6.60-28.99	2383.64 1620.48-3287.06	29.40 17.28-37.34
INF 1b 1 month	1.0 0-3.5	12.35 5.73-31.63	2362.09 1673.86-2866.10	19.32 <sup>*</sup> 14.97-28.79
INF 1b 6 months	1.0 0-3.0	14.70 7.89-25.13	1318.68 5.91-29.75	13.90 <sup>**</sup> 11.05-18.98

<sup>\*</sup>P<0.0001 (1 month vs. baseline),

<sup>\*\*</sup>P<0.0001 (6 months comparing to baseline and to 1 month).

**Table 3:** The effects of interferon 1b treatment on adipocytokines concentrations.

	EDSS	Leptin [ng/ml]	Adiponectin [ng/ml]	Resistin [ng/ml]
GA baseline	1.0 0-2.0	19.16 ± 14.49	1978.21 1409.95-3643.83	36.61 30.16-46.55
GA 1 month	1.0 0-2.0	20.62 ± 14.27	1647.22 1352.15-3782.36	36.17 28.18-51.55
GA 6 month	1.0 0-2.0	14.59 ± 12.32	2265.35 1374.58-3596.76	24.43 <sup>*</sup> 19.22-28.88

<sup>\*</sup>P=0.011

**Table 4:** The effects of glatiramer acetate treatment on adipocytokines concentrations.

resistin and adiponectin concentrations result from immune response only. Only a few reports on resistin levels in MS patients exist [15,16] that are in accordance with our results. However, no data are available on the role of resistin in immune response in myasthenia gravis. The pathogenesis of MS and MG is absolutely different, thus the elevation in resistin may also be considered as a secondary effect. In humans, the highest resistin expression was found in bone marrow and it is up-regulated approximately 4-fold during the differentiation of monocytes to macrophages [22]. Resistin mRNA was detected in peripheral blood mononuclear cells (PBMC) [23]. Proinflammatory cytokines like interleukin 1 (IL-1), IL-6, and TNF- $\alpha$  up-regulate resistin expression in PBMC [24]. During the pathogenesis of multiple sclerosis, monocytes and macrophages are considered to be involved in both brain injury and repair. The clearance of myelin debris by macrophage phagocytosis in demyelinating lesions is required for effective remyelination [25]. The phagocytosis of myelin modulates the function of macrophages and monocytes [26,27] and furthermore suppresses lymphocyte proliferation triggered by T cell receptors in an antigen-independent manner [28]. In the light of those results, an increase in resistin concentrations may reflect the activation of monocytes/macrophages in RRMS patients. Similarly, during the course of myasthenia gravis, increased resistin concentrations may result from the stimulation of monocytes/macrophages. In experimental myasthenia gravis, large suppressive macrophages inhibited the proliferation of T cells and induced their apoptosis [29]. Moreover, monocytes/macrophages, together with dendritic cells and B cells, have recently been found inside and around the high endothelial venules in myasthenic thymic [30].

In our study, adiponectin concentration was increased in RRMS patients compared to controls; however, it was lower than in MG individuals. The higher adiponectin concentrations detected in the cerebrospinal fluid of MS patients, without a significant increase in serum, suggests it is intrathecally produced and involved in MS pathogenesis [17]. Recently, in an experimental study [31], it was shown that adiponectin deficient mice develop EAE with more severe inflammation, demyelination, and axonal injury associated with the increased production of interferon  $\gamma$  (IFN- $\gamma$ ), interleukin 17 (IL-17), TNF- $\alpha$ , and IL-6 by lymphocytes and a decreased number of regulatory

T cells. There are no available reports on the role of adiponectin in myasthenia gravis.

The present study focused on the effect RRMS treatment has on the concentration of adipocytokines. Routine treatment of MS relapse with methylprednisolone induces an unfavorable effect leading to the increase of leptin concentration. Experimental studies showed similar effects of methylprednisolone infusion on plasma leptin concentration [32] with subsequent metabolic effects in adipose tissue and skeletal muscles leading to limitation of insulin-mediated glucose utilization. In another experimental study, the peak plasma leptin concentration appeared 12 hours after methylprednisolone infusion [33]. In humans with Graves' hyperthyroidism ophthalmopathy treated with methylprednisolone, plasma leptin levels were elevated already at the eighth hour and lasted for 72 hours after infusion [34]. However, in non-obese, non-diabetic healthy individuals, a single intravenous dose of methylprednisolone followed by 4 day oral administration did not affect the plasma levels of leptin [35]. Thus, the effect of methylprednisolone on leptin levels seems to be stronger in humans with autoimmune disorders like RRMS. Moreover, in our study, resistin concentration positively correlated with HOMA-IR insulin resistance index in methylprednisolone treated RRMS patients. This observation suggests an increased risk for insulin resistance in RRMS patients during methylprednisolone treatment.

We have found that interferon-1b treatment causes a beneficial and time-dependent effect on resistin concentration in RRMS patients. We are not aware of any studies on interferon treatment on resistin concentrations in RRMS patients. Only recently did any experimental study exist in which the stimulation of interferon alpha and beta lead to the decreased expression of leptin, adiponectin, and resistin in adipose tissue [36]. Adiponectin and leptin concentrations were not influenced by interferon treatment in our study. Batocchi et al. suggested that leptin may be a marker of MS activity and its response to therapy, because of a lowering effect interferon treatment has on leptin levels [20]. We have not found such an effect; however, the disability of our MS cohort measured with the EDSS was less severe compared to Batocchi's group. Thus, the effect of interferon treatment on adipocytokines may depend on disease severity. This suggestion is supported by a report that showed no effect of interferon beta treatment on leptin levels in patients who had secondary progressive multiple sclerosis (SPMS), a beneficial influence on leptin concentrations was observed only in patients who did not have progression in disability [37]. Both interferon beta and glatiramer acetate did not show any effect on adiponectin concentration in our study and such an observation was also reported by Musabak et al. [19]. Moreover, we did not notice an effect of glatiramer acetate on leptin concentration. We have found a beneficial effect of glatiramer acetate on resistin concentration in our RRMS patients. To the best of our knowledge this is the first report on resistin level modification by glatiramer acetate. This finding may be of particular importance because resistin gene polymorphisms have been suggested to be involved in MS pathogenesis [16].

We did not detect a relationship between EDSS score, localization of demyelinating plaques on MRI scans, or HOMA-IR insulin resistance index and adipocytokine concentrations in RRMS patients treated with first-line immunomodulatory drugs. This can be explained by the low disability in our patients, reflected by their low EDSS scores. As a result, the effect of treatment can only be observed at the molecular level, and not with clinical measures. Similarly, in another study [19], the authors did not find a correlation between adiponectin concentration and EDSS score.

To conclude, we identified resistin as the most important adipocytokine to be associated with RRMS patients. Its concentrations are reduced by first line immunomodulatory treatment of RRMS, which produces a beneficial milieu of inflammatory and metabolic processes. On the other hand, the routine treatment of MS relapse with methylprednisolone induces harmful metabolic and inflammatory effect leading to an increase in leptin levels.

## References

1. Tilg H, Moschen AR (2006) Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol* 6: 772-783.
2. Matarese G, Procaccini C, De Rosa V (2008) The intricate interface between immune and metabolic regulation: a role for leptin in the pathogenesis of multiple sclerosis? *J Leukoc Biol* 84: 893-899.
3. Zhang Y, Proenca R, Maffei M, Barone M, Leopold et al. (1994) Positional cloning of the mouse obese gene and its human homologue. *Nature* 372: 425-432.
4. Gainsford T, Willson TA, Metcalf D, Handman E, McFarlane C, et al. (1996) Leptin can induce proliferation, differentiation, and functional activation of hemopoietic cells. *Proc Natl Acad Sci U S A* 93: 14564-14568.
5. Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, et al. (1998) Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. *Nature* 394: 897-901.
6. Silswal N, Singh AK, Aruna B, Mukhopadhyay S, Ghosh S, et al. (2005) Human resistin stimulates the pro-inflammatory cytokines TNF-alpha and IL-12 in macrophages by NF-kappaB-dependent pathway. *Biochem Biophys Res Commun* 334: 1092-1101.
7. Son YM, Ahn SM, Kim GR, Moon YS, Kim SH, et al. (2010) Resistin enhances the expansion of regulatory T cells through modulation of dendritic cells. *BMC Immunol* 11: 33.
8. Stepan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, et al. (2001) The hormone resistin links obesity to diabetes. *Nature* 409: 307-312.
9. Kim KH, Zhao L, Moon Y, Kang C, Sul HS (2004) Dominant inhibitory adipocyte-specific secretory factor (ADSF)/resistin enhances adipogenesis and improves insulin sensitivity. *Proc Natl Acad Sci U S A* 101: 6780-6785.
10. Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, et al. (2007) Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. *Nat Med* 13: 332-339.
11. Saijo S, Nagata K, Nakano Y, Tobe T, Kobayashi Y (2005) Inhibition by adiponectin of IL-8 production by human macrophages upon coculturing with late apoptotic cells. *Biochem Biophys Res Commun* 334: 1180-1183.
12. Matarese G, Di Giacomo A, Sanna V, Lord GM, Howard JK, et al. (2001) Requirement for leptin in the induction and progression of autoimmune encephalomyelitis. *J Immunol* 166: 5909-5916.
13. Sanna V, Di Giacomo A, La Cava A, Lechler RI, Fontana S, et al. (2003) Leptin surge precedes onset of autoimmune encephalomyelitis and correlates with development of pathogenic T cell responses. *J Clin Invest* 111: 241-250.
14. De Rosa V, Procaccini C, La Cava A, Chieffi P, Nicoletti GF, et al. (2006) Leptin neutralization interferes with pathogenic T cell autoreactivity in autoimmune encephalomyelitis. *J Clin Invest* 116: 447-455.
15. Kraszula L, Jasinska A, Eusebio M-O, Kuna P, Glabinski A et al. (2012) Evaluation of the relationship between leptin, resistin, adiponectin and natural regulatory T cells in relapsing-remitting multiple sclerosis. *Neurol Neurochir Pol* 46: 22-28.
16. Hossein-Nezhad A, Varzaneh FN, Mirzaei K, Emamgholipour S, Varzaneh FN, et al. (2013) A polymorphism in the resistin gene promoter and the risk of multiple sclerosis. *Minerva Med* 104: 431-438.
17. Hietaharju A, Kuusisto H, Nieminen R, Vuolteenaho K, Elovaara I, et al. (2010) Elevated cerebrospinal fluid adiponectin and adipisin levels in patients with multiple sclerosis: a Finnish co-twin study. *Eur J Neurol* 17: 332-334.
18. Palavra F, Marado D, Mascarenhas-Melo F, Sereno J, Teixeira-Lemos E, et al. (2013) New markers of early cardiovascular risk in multiple sclerosis patients: oxidized-LDL correlates with clinical staging. *Dis Markers* 34: 341-348.
19. Musabak U, Demirkaya S, Genç G, Ilikci RS, Odabasi Z (2011) Serum adiponectin, TNF- $\alpha$ , IL-12p70, and IL-13 levels in multiple sclerosis and the effects of different therapy regimens. *Neuroimmunomodulation* 18: 57-66.
20. Batocchi AP, Rotondi M, Caggiula M, Frisullo G, Odoardi F, et al. (2003) Leptin as a marker of multiple sclerosis activity in patients treated with interferon-beta. *J Neuroimmunol* 139: 150-154.
21. Sellebjerg F, Barnes D, Filippini G, Midgard R, Montalban X et al. (2011) Acute relapses of multiple sclerosis: European Handbook of Neurological Management. Blackwell Publishing Ltd.
22. Patel L, Buckels AC, Kinghorn IJ, Murdock PR, Holbrook JD, et al. (2003) Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. *Biochem Biophys Res Commun* 300: 472-476.
23. Savage DB, Sewter CP, Klenk ES, Segal DG, Vidal-Puig A, et al. (2001) Resistin/Fizz3 expression in relation to obesity and peroxisome proliferator-activated receptor-gamma action in humans. *Diabetes* 50: 2199-2202.
24. Kaser S, Kaser A, Sandhofer A, Ebenbichler CF, Tilg H, et al. (2003) Resistin messenger-RNA expression is increased by proinflammatory cytokines in vitro. *Biochem Biophys Res Commun* 309: 286-290.
25. Kotter MR, Zhao C, van Rooijen N, Franklin RJ (2005) Macrophage-depletion induced impairment of experimental CNS remyelination is associated with a reduced oligodendrocyte progenitor cell response and altered growth factor expression. *Neurobiol Dis* 18: 166-175.
26. van Rossum D, Hilbert S, Strassenburg S, Hanisch UK, Brück W (2008) Myelin-phagocytosing macrophages in isolated sciatic and optic nerves reveal a unique reactive phenotype. *Glia* 56: 271-283.
27. Gredler V, Ebner S, Schanda K, Forstner M, Berger T, et al. (2010) Impact of human myelin on the maturation and function of human monocyte-derived dendritic cells. *Clin Immunol* 134: 296-304.
28. Bogie JF, Stinissen P, Hellings N, Hendriks JJ (2011) Myelin-phagocytosing macrophages modulate autoreactive T cell proliferation. *J Neuroinflammation* 8: 85.
29. McIntosh KR, Drachman DB (1999) Induction of apoptosis in activated T cell blasts by suppressive macrophages: a possible immunotherapeutic approach for treatment of autoimmune disease. *Cell Immunol* 193: 24-35.
30. Weiss JM, Cufi P, Bismuth J, Eymard B, Fadel E, et al. (2013) SDF-1/CXCL12 recruits B cells and antigen-presenting cells to the thymus of autoimmune myasthenia gravis patients. *Immunobiology* 218: 373-381.
31. Piccio L, Cantoni C, Henderson JG, Hawiger D, Ramsbottom M, et al. (2013) Lack of adiponectin leads to increased lymphocyte activation and increased disease severity in a mouse model of multiple sclerosis. *Eur J Immunol* 43: 2089-2100.
32. Fang J, Sukumaran S, Dubois DC, Almon RR, Jusko WJ (2013) Meta-modeling of methylprednisolone effects on glucose regulation in rats. *PLoS One* 8: e81679.
33. Sukumaran S, Jusko WJ, DuBois DC, Almon RR (2011) Mechanistic modeling of the effects of glucocorticoids and circadian rhythms on adipokine expression. *J Pharmacol Exp Ther* 337: 734-746.
34. Song YM, Lee WJ, Chen MD, Kao CH, Sheu WH (2000) Methylprednisolone increases plasma leptin levels in Graves' hyperthyroidism patients with active Graves' ophthalmopathy. *Horm Metab Res* 32: 277-282.
35. Tataranni PA, Pratley R, Maffei M, Ravussin E (1997) Acute and prolonged administration of glucocorticoids (methylprednisolone) does not affect plasma leptin concentration in humans. *Int J Obes Relat Metab Disord* 21: 327-330.
36. Yu L, Yan K, Liu P, Li N, Liu Z, et al. (2014) Pattern recognition receptor-initiated innate antiviral response in mouse adipose cells. *Immunol Cell Biol* 92: 105-115.
37. Angelucci F, Mirabella M, Caggiula M, Frisullo G, Patanella K, et al. (2005) Evidence of involvement of leptin and IL-6 peptides in the action of interferon-beta in secondary progressive multiple sclerosis. *Peptides* 26: 2289-2293.

**Citation:** Michalak S, Jernas L, Wysocka E, Osztynowicz K, Kupczyk ET, et al. (2014) The Effect of Methylprednisolone, Interferon Beta and Glatiramer Acetate Treatment on the Levels of Leptin, Adiponectin and Resistin in Multiple Sclerosis Patients. *J Neurol Neurophysiol* S12: 005. doi:10.4172/2155-9562.S12-005