Abstract Title: Body Mass Index and Multiple Sclerosis Risk. The Role of Leptin.

Press Release Title: Do Obesity, Birth Control Pills Raise Risk of Multiple Sclerosis?

Objective: To examine whether body mass index (BMI) is associated with higher risk of developing MS, and to study how excess weight could alter immune tolerance.

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Background: Obesity is associated with a chronic inflammatory state and cytokine release, ultimately affecting immune responses. Leptin, aside from its effect on metabolism is also a member of the long-chain helical cytokine family, suggesting a possible link between nutritional status and immune function.

Design/Method: BMI was calculated in 210 MS patients and in 210 age- and gender-matched control subjects at age 15 and 20 years, and at the present time. Leptin, 25-(OH) Vitamin D, Bcl-2, P21, P27 kip, STAT3 and SOCS3 were measured by ELISA. IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-15, IL-21,TNF-α and IFN-γ production were evaluated using ELISPOT. CD4+CD25+FoxP3+ Treg cells were assessed using flow cytometry.

Results: Obesity at 20 years of age (BMI > 30kg/m2) was associated with higher risk of developing MS (OR 2.1, 95% CI 1.2-3.7, p=0.02). BMI correlated directly with serum leptin levels, and inversely with 25(OH) Vitamin D levels. Obese MS patients showed higher number of IL-1α, IL-2, IL-6, IL-15, IL-17, IFN-γ and TNF-α producing cells, compared to non-obese MS subjects. Moreover, leptin increased MBP-peptide specific CD4+ T cell proliferation, and inhibited apoptosis induction through increased expression of Bcl-2. Obese patients showed reduced numbers of CD4+CD25+FoxP3+ Treg cells. Furthermore, leptin induced hyporesponsiveness of CD4+CD25+FoxP3+ Treg cells, a phenomenon associated with increased expression of p-STAT3, p21 and p27kip, and lower expression of SOCS3. All these effects were reversed by leptin neutralization or leptin receptor inhibition.

Conclusions: 1). Obesity in adolescence/early adulthood is associated with increased risk of MS. 2). Leptin exerts opposite effects on regulatory and CD4+ effector T cells, promoting inflammatory responses, potentially representing a putative link between obesity and autoimmunity in MS.

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