BODY MASS INDEX IN MULTIPLE SCLEROSIS: ASSOCIATION WITH SERUM LEPTIN

Thesis

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List of Abbreviations

Abb.	Full term
6MW	*6-minute walk*
ANOVA	*Analysis of variance*
AQP4	*Aquaporin 4*
AUC	*Area Under The Curve*
BMI	*Body Mass Index*
CD8	*Cluster of Differentiation 8 cell*
CD4	*Cluster of Differentiation 4 cell*
CIS	*Clinically Isolated Syndrome*
CNS	*Central Nervous System*
CSF	*Cerebro-Spinal fluid*
Cw	*Oxygen Cost of Walking*
DALYs	*Disability-Adjusted Life Years*
DCs	*Dendritic Cells*
DIS	*Dissemination In Space*
DIT	*Dissemination In Time*
DMT	*Disease Modifying Treatment*
EAE	*Experimental Autoimmune Encephalomyelitis*
EBV	*Epstein Bar Virus*
EDSS	*Extended Disability Status Scale*
FDCs	*Follicular Dendritic Cells*
FOXP3	*Fork-Head box P3 protein*
GIANT	*Genetic Investigation of Anthropometric Traits*
GWASs	*Genome-Wide Association Studies*
HDL	*High Density Lipoprotein*
HHV	*Human Herpes Virus*

List of Abbreviations cont...

Abb.	Full term
HLA	*Human Leukocyte Antigen*
IFN-b	*Interferon-beta*
IFN-g	*Interferon-gamma*
IgG	*Immuno-globulin G*
IL	*Inter-Leukin*
IQR	*Interquartile Range*
KDa	*Kilo-daltons (Molecular weight)*
Kg	*Kilograms*
LT	*Leukotrien*
m2	*Meter Squared*
MAGNIMS	*Magnetic Resonance Imaging In MS*
MENA	*Middle East and North Africa*
MHC	*Major Histo-compatibility Complex*
MRI	*Magnetic Resonance Imaging*
MS	*Multiple Sclerosis*
MSWS-12	*Multiple Sclerosis Walking Scale-12*
NHANES	*National Health and Nutrition Examination Survey*
NMO	*Neuro-Myelitis Optica*
Ob gene	*Obesity gene*
OB-R	*Obesity gene receptor*
PBMCs	*Peripheral Blood Mono-nuclear Cells*
PDDS	*Patient Determined Disease Steps*
Pg	*picogram*
PHA	*Phyto-haemagglutinin*
PP	*Primary Progressive*
PR	*Progressive Relapsing*

List of Abbreviations cont...

Abb.	Full term
RR	*Relapsing Remitting*
P-value	*Probability value*
SD	*Standard deviation*
SEP	*Socio-Economic Position*
SPMS	*Secondary Progressive Multiple Sclerosis*
T25FW	*Timed 25 Feet Walk*
TCR	*T Cell Receptor*
TGF	*Transforming Growth Factor*
Th	*T helper*
TNF	*Tumour Necrosis Factor*
T-reg	*T Regulatory cell*
USA	*United States of America*
WAT	*White Adipose Tissue*
WHO	*World Health Organization*

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INTRODUCTION

Multiple sclerosis (MS) is an inflammatory demyelinating and neurodegenerative disease affecting more than 2 million people worldwide ***(Heydarpour et al., 2015).***

Multiple sclerosis is a relatively common disease in Europe, the United States, Canada, New Zealand, and parts of Australia. Incidence is low in childhood, increases rapidly after the age of 18, reaches a peak between 25 and 35 years (about 2 years earlier in women than men), and then slowly declines, becoming rare at age 50 and older. The female-to-male ratios are between 1.5 and 2.5 in most populations ***(Ascherio and Munger, 2007).***

Middle Eastern and North African countries are located in a low- to moderate-risk zone for MS based on the 2013 MS Atlas ***(Browne et al., 2014).***

A community-based survey in Al Quseir, Egypt, has found an MS prevalence of 13.74/100,000 ***(Tallawy et al., 2013).***

Multiple sclerosis is a debilitating autoimmune disease of the central nervous system that results in chronic disability for the majority of those affected ***(Compston and Coles, 2008).*** It is a leading cause of non-traumatic disability in young adults in many countries ***(Heydarpour et al., 2015).*** The disease has an important impact on the health economy of many countries

(Trisolini et al., 2010), since current treatment regimens are costy and have adverse side-effect profiles and/or limited efficacy ***(Hartung et al., 2015).***

Four MS clinical courses are recognized: relapsing remitting (RR), secondary progressive (SP), primary progressive (PP), and progressive relapsing (PR). CIS is recognized as the first clinical presentation of a disease that shows characteristics of inflammatory demyelination that could be MS, but has yet to fulfill criteria of dissemination in time ***(Lublin et al., 2014).***

In patients with the relapsing– remitting phase of the disease the disease begins with acute episodes of neurologic dysfunction, followed by periods of partial or complete remission with clinical stability between relapses ***(Lublin and Reingold, 1996).***

SPMS is diagnosed retrospectively by a history of gradual worsening after an initial relapsing disease course, with or without acute exacerbations during the progressive course. PPMS is a part of the spectrum of progressive MS phenotypes with absence of exacerbations prior to clinical progression ***(Lublin et al., 2014).***

Multiple sclerosis is characterized by multi-centric inflammation and demyelination of the central nervous system, but the role of axonal injury and gliosis increases as the disease evolves ***(Trapp et al., 1998).***

MS is believed to be an autoimmune disease because inflammatory infiltrates of the CNS contain T and B lymphocytes ***(Esiri and Gay, 1997)***.

Genetic susceptibility has been linked to MHC class II genes ***(McFarland et al., 1997).*** Although genetic susceptibility explains the clustering of MS cases within families and the sharp decline in risk with increasing genetic distance, it cannot fully explain the geographic variations in MS frequency and the changes in risk that occur with migration ***(Ascherio and Munger, 2007).***

Disparities in environmental risk factors and genetic predispositions modulate the risk of MS at the population level ***(Ebers, 2008).***

MS risk is about 10 times greater among individuals who experienced an undiagnosed EBV infection in childhood. Vitamin D is emerging as an important protective cofactor against MS. Other risk factors are involved in the pathogenesis of MS as: cigarette smoking, Diet, Hormones, and Other Factors ***(Ascherio and Munger, 2007).***

Increased body mass index (BMI) at the age of 18 is associated with a two-fold increase in the risk of MS ***(Munger et al., 2009).***

Obesity has been associated with a chronic inflammatory state, due to the secretion of pro-inflammatory proteins in the blood ***(Ouchi et al., 2012).***

A potential reason for the impact of obesity on disease is the associated increase in adipokines, a family of molecules with effects on inflammatory and autoimmune diseases ***(Tilg and Moschen, 2006).***

Leptin, a cytokine-like hormone released primarily from adipocytes, exhibits neuroendocrine properties influencing energy balance. Serum leptin levels regulate body weight by inhibiting food intake and stimulating energy expenditure and are higher in subjects with a high BMI and body fat ***(Ostlund et al., 1996).***

The obese (ob) gene product of leptin is a 16 kDa protein secreted by white adipose tissues. It regulates food intake, body weight and maintains energy homeostasis via interactions in the brain, mainly the hypothalamus ***(Harvey, 2007).*** However the functions of leptin are not confined to the hypothalamus, with leptin receptors found in various regions of the brain not generally associated with energy balance, including the cortex, thalamus, cerebellum, brain stem, basal ganglia, olfactory tract and hippocampus ***(Harvey, 2007; Pan and Kastin, 2014).*** The wide distribution of leptin receptors points a potential role for leptin in modulating widespread biological actions in the CNS.