sciendo

ENDOCRINE REGULATIONS, Vol. 52, No. 3, 139–145, 2018

doi:10.2478/enr-2018-0017

LDL and HDL lipoprotein subfractions in multiple sclerosis patients with decreased insulin sensitivity

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Objectives. Increased metabolic and cardiovascular morbidity has been reported in multiple sclerosis (MS) patients. Previously, we have found decreased insulin sensitivity and hyperinsulinemia in a group of newly diagnosed MS patients. We hypothesize that these features may be associated with an altered lipid profile and low, intermediate, or high density lipoprotein (LDL, IDL, HDL) subclasses accelerating atherosclerosis and thus contributing to the cardiovascular risk increase in these patients.

Subjects and methods. In a group of 19 newly diagnosed untreated MS patients with previously found hyperinsulinemia and insulin resistance and a matched group of 19 healthy controls, the lipoprotein subclasses profile was determined. Polyacrylamide gel electrophoresis was used to separate and measure the LDL (large LDL and small dense LDL), HDL (large, intermediate and small), and IDL (A, B and C) subclasses with the Lipoprint© System (Quantimetrix Corporation, Redondo Beach, CA, USA).

Results. No difference was found either in the conventional lipid or lipoprotein subclasses profile between the MS patients and healthy controls. We found an inverse association between the level of IDL-B with fasting insulin (r=–0.504, p=0.032), the insulin resistance estimated by homeostatic model assessment – insulin resistance (HOMA-IR) (r=–0.498, p=0.035), insulin response expressed as area under the curve (AUC; r=–0.519, p=0.027), and area above the baseline (AAB; r=–0.476, p=0.045) and positive association with insulin sensitivity estimated by insulin sensitivity index (ISI) Matsuda (r=0.470, 0.048) in MS patients, but not in healthy controls suggesting the first signs in lipoprotein subclasses profile change.

Conclusions. Our data indicate that changes in lipoprotein profile and subclasses are preceded by insulin resistance and hyperinsulinemia in patients with newly diagnosed MS.

Key words: multiple sclerosis, insulin resistance, lipoproteins, cholesterol

Patients suffering from the multiple sclerosis (MS) have been reported to be in an increased risk of the metabolic and cardiovascular comorbidities, such as atherosclerosis, hypertension, obesity, and metabolic syndrome (MetS) (Sicras-Mainar et al. 2017). MetS is a complex disorder characterized by a cluster of interconnected factors (dyslipidemia, elevated blood pressure, abdominal obesity, dysregulated glucose metabolism, and insulin resistance) leading to an increased risk of cardiovascular diseases and diabetes mellitus type 2 (Kassi et al. 2011). Previous research of chronic inflammatory diseases, such as autoim-

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mune diseases, has shown a strong association between the dyslipidemia and cardiovascular risk and higher prevalence of MetS in the rheumatoid arthritis and systemic lupus erythematosus (Torres et al. 2009; Boyer et al. 2011; Versini et al. 2014). However, the data of MetS risk factors for MS patients are limited and inconsistent suggesting an increased cardiovascular risk, however, without identifying the causal relationship to the obesity or body composition, hypertension, type 2 diabetes or dyslipidemia in MS patients (Wens et al. 2013; Guerrero-Garcia et al. 2016). Information on the effect of serum triglycerides and cholesterol levels and the roles of HDL and LDL levels on the MS disease progression are limited suggesting an association between the lipoprotein profile and disease progress in MS patients (Weinstock-Guttman et al. 2011). Association with the blood-brain barrier function, impairment, formation of new lesions, and disability progression have been speculated (Tettey et al. 2014; Fellows et al. 2015).

In our previous study, we have found decreased insulin sensitivity and hyperinsulinemia unrelated to inflammatory and physical activity status in patients with MS (Penesova et al. 2015). Insulin resistance, typically associated with the dyslipidemia, has a noticeable effect on the lipoprotein size and levels of VLDL, LDL, and HDL subfractions (Krauss 2004).

The relationship of dyslipidemia, namely of elevated total cholesterol, LDL-cholesterol and decreased HDL-cholesterol levels to atherogenesis and cardiovascular diseases is well accepted. However, the major lipoprotein classes represent a heterogeneous group of particles that differ by density, particle size, migration characteristics, apoprotein content, and relationships to disease, i.e. parameters not measurable by the conventional lipid panel. It has been suggested that the different subfractions may vary in their risk profile. Thus, patients with the same even normal LDL and HDL levels may be at different cardiovascular risk. Generally, HDL is considered to have protective antiatherogenic effects. Large HDL (L-HDL) appear to contribute more to the cardioprotective effects of high HDL cholesterol than the small one (Krauss 2004). Small HDL (S-HDL) subfractions are associated with increased risk of atherosclerosis and coronary heart disease (Garvey et al. 2003; Asztalos et al. 2004). Similarly, small dense LDL particles are associated with an increased risk of cardiovascular diseases, metabolic syndrome, and diabetes, whereby large LDL subfractions are not associated with the cardiovascular risk (Garvey et al. 2003; Krauss 2004).

In this study, taking into consideration the above mentioned background and the limited information availability on the link between the insulin resistance, dyslipidemia, and the pathogenesis of MS, we aimed to assess the associations of serum lipid profile variables to insulin sensitivity and anthropometric parameters in a group of newly diagnosed MS patients and healthy controls. We assume that the decreased insulin sensitivity, found in this group of SM patients, may be associated with a shift in the lipoprotein subfractions' profile, in a way of increased atherogenic small LDL- and HDL-subfractions and may contribute to the increased cardiovascular risk in the MS patients.

Subjects and methods

Subjects. We studied 19 patients with MS who were recruited from the registry of the 1st Department of Neurology, Medical Faculty, Comenius University, Bratislava, Slovakia. All tests and analyses were performed in patients fulfilling the inclusion/exclusion criteria [diagnosis of MS according to McDonald's criteria after a first episode of symptoms, an Expanded Disability Status Scale (EDSS) score ≤ 2.0, aged 20–45 years, without any history of cardiovascular, metabolic, endocrine, renal or hepatic disease, current smoking, malignancy, acute or chronic infection or any current medication]. The examinations were performed at least 2 months after the pulse glucocorticoid treatment (methylprednisolone 1000 mg per day i.v. for 3–5 days) of the first MS episode; at the time of examination all patients were in remission and without any medication. Age, sex and body mass index (BMI) matched healthy volunteers served as controls. Physical activity as well as systemic inflammation markers [interleukin-6 (IL-6), tumor necrosis factor (TNF) and high sensitivity C-reactive protein (hsCRP)] were comparable in MS patients and healthy controls (Penesova et al. 2015). Clinical characteristics of the groups are shown in Table 1. The study was carried out according to the ethical standards of the National Research Committee and to the 1964 Helsinki declaration and its later amendments or comparable ethical standards. After detailed explanation, all patients and controls signed informed consent before participating in the study. The study was approved by the Ethics Committee of the Bratislava Self-Governing Region, Bratislava, Slovakia.

Study protocol. Detailed study protocol has been described elsewhere (Penesova et al. 2015). Briefly, the subjects reported to the laboratory at 08:00 AM after an overnight fasting. Upon arrival, personal medical history and anthropometric measures [body height, weight, body fat percentage using bioelectri-

cal impedance (Omron 511BF, Omron Healthcare Co., Ltd., Kyoto, Japan), and waist circumference] were recorded, blood pressure (Dinamap Vital Sign Monitor 845 XT, Criticon X, Inc., Tampa, FL, USA) was measured. Cubital vein was cannulated for blood sampling. An oral glucose tolerance test (OGTT) was performed. After the first baseline blood sample was taken (0 min), the subjects ingested over 3 min a solution containing 75 g glucose in 250 ml water. Further blood samples were taken every 15 min over 2 h, centrifuged at 4 °C and aliquots of serum and EDTA plasma were stored frozen at –70 °C until assayed.

Assays and calculations. Plasma glucose concentrations and fasting serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), and triglyceride (TG) levels were determined using an autoanalyzer (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) by standard procedure with enzymatic kits (Roche Diagnostics, Lewes, UK). Plasma insulin levels were measured by ELISA kits (ALPCO Diagnostics, Salem, NH, USA). Insulin sensitivity/resistance indices were calculated using fasting (Matthews et al. 1985) and OGTT-derived glucose and insulin concentration (Cederholm and Wibell 1990; Matsuda and DeFronzo 1999) as described previously by Penesova et al. (2015). To compare insulin response to oral glucose load, Area Under the Curve (AUC) and Area Above the Baseline (AAB) were calculated using a trapezoidal rule.

Lipoprotein subfraction analysis was performed using high resolution polyacrylamide gel electrophoresis technique – Lipoprint system (Quantimetrix Corporation, Redondo Beach, CA, USA) according to the manufacturer's manual, which enabled to analyse the following lipoprotein subfractions profile: the very low-density lipoprotein (VLDL) fraction, the intermediate-density lipoprotein (IDL) C, B and A, the low-density lipoprotein (LDL) with subfractions 1 and 2 (large LDL) and subfractions 3 to 7 (small dense LDL – sdLDL), and the high density lipoprotein (HDL) subfractions categorized into large (subfraction 1–3), intermediate (subfraction 4–7), and small HDL (subfraction 8–10).

Statistical evaluation. Data were statistically evaluated using the SPSS statistical program (SPSS Inc., Chicago, IL, USA). The normality of continuous variables was assessed by the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean ± SD, while data not normally distributed were expressed as median (interquartile range [IQR]). The comparisons of the continuous variables between the groups were evaluated by Student's t-test or Mann-Whitney's U test, as appropriate. Associations between the lipid and insulin sensitivity parameters were assessed by Pearson's or Spearman's correlation coefficient depending on the normality of data. Differences were considered significant at $p<0.05$.

Results

General characteristics of the study groups, as shown in Table 1, have been adapted from our previous article (Penesova et al. 2015). The MS patients and healthy controls were very well matched for the

Table 1
Clinical characteristics, lipid profile, plasma glucose, insulin, insulin response and calculated indices of insulin sensitivity/resistance in MS patients compared to age, sex and BMI matched healthy controls

Parameter	MS (n=19)	Controls (n=19)
Men/women	9/10	9/10
Age (years)	30.4±7.1	28.7±6.7
BMI (kg/m^2)	23.7±4.5	24.4±5.3
EDSS (arbitrary units)	1.1±0.7	–
Body fat percentage (%)	27.1±7.6	27.8±7.6
Lean body mass (kg)	52.3±11.3	54.9±13.3
SBP (mmHg)	114±12/111 (107–115)	118±13/114 (110–132)
DBP (mmHg)	70±8	73±9
Heart rate (beats/min)	67±11	70±10
Triglycerides (mmol/l)	0.89±0.51	1.02±0.64
Total cholesterol (mmol/l)	4.56±0.92	4.08±0.72
HDL cholesterol (mmol/l)	1.48±0.35	1.37±0.41
LDL cholesterol (mmol/l)	2.45±0.79	2.34±0.61
Fasting glucose (mmol/l)	5.18±0.29	4.96±0.37
Fasting insulin (mU/l)	5.64±5.20/4.50 (3.09–5.55)	3.95±2.63/3.00 (1.86–5.52)
AUC insulin (mU·min·l^{-1})	6375±2422	4562±2355*
AAB insulin (mU·min·l^{-1})	5699±2181	4088±2089*
HOMA–IR	1.33±1.28/1.04 (0.74–1.31)	0.90±0.62/0.66 (0.38–1.32)
ISI Matsuda	6.94±3.44	10.61±4.81**
ISI Cederholm	50±15	61±16*

Normally distributed data are expressed as mean±S.D. Not normally distributed data are expressed as median (interquartile range) as well. *p≤0.05; **p≤0.01. Abbreviations: MS – multiple sclerosis; BMI – body mass index; EDSS – Expanded Disability Status Scale; SBP – systolic blood pressure; DBP – diastolic blood pressure; HDL – high density lipoprotein; LDL – low density lipoprotein; AUC – area under the curve; AAB – area above baseline; HOMA-IR – homeostatic model assessment – insulin resistance; ISI – insulin sensitivity index.

age, BMI, and body fat percentage (BF%). The EDSS score in MS patients was 1.1±0.7, normal neurological findings or only minimal neurological sings without disability were present. There was no difference in the blood pressure, heart rate, and lipid parameters (total cholesterol, HDL, LDL, triglycerides), as well as in measured lipoprotein subclasses between patients and controls (Table 2). Decreased peripheral (ISI Cederholm, p=0.03) and whole body (ISI Matsuda, p=0.01) insulin sensitivity has been described previously (Penesova et al. 2015). Insulin response to oral glucose load (expressed as AUC and AAB) was significantly higher (p<0.05) in MS patients when compared to healthy subjects (Table 1).

All lipoprotein subfractions measured were comparable in MS patients and healthy controls (Table 2). Correlations of lipoprotein subfractions with anthropometric [age, BMI, BF%, fat mass (FM)] and cardiometabolic [systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), fasting glucose, fasting insulin, AUC insulin, AAB insulin, IR HOMA, ISI Matsuda, ISI Cederholm) parameters in all subjects studied (MS patients and controls combined) brought only the positive correlation of IDL-A and age (r=0.347, p=0.035).

Table 2
Lipoprotein subfractions in MS patients compared to age, sex and BMI matched healthy controls

Parameter	MS (n=19)	Controls (n=19)
VLDL (mg/dl)	29.3±12.7	26.0±7.2
IDL-A (mg/dl)	8.4±4.1	8.4±3.3
IDL-B (mg/dl)	11.4±6.0/10 (8–12)	10.5±6.9/9 (7–11)
IDL-C (mg/dl)	34.2±9.4	32.3±7.7
LDL1 (mg/dl)	13.9±10.5	15.6±8.9
LDL2 (mg/dl)	8.6±9.7	7.7±8.4
LDL1-2 (mg/dl)	22.6±18.9	23.4±16.0
LDL3-7 (mg/dl)	2.22±6.36/0 (0–2)	2.11±6.40/0 (0–1.5)
Large HDL (mg/dl)	35.4±21.4	27.4±10.5
Intermediate HDL (mg/dl)	26.6±5.7	24.0±4.4
Small HDL (mg/dl)	4.28±3.27	3.47±2.78
Total cholesterol (mg/dl)	175±37	157±28

Normally distributed data are expressed as mean±S.D. Not normally distributed data are expressed as median (interquartile range) as well. Abbreviations: MS – multiple sclerosis; BMI – body mass index; VLDL – very low density lipoprotein; IDL – intermediate density lipoprotein; LDL – low density lipoprotein; HDL – high density lipoprotein.

In MS patients, IDL-A correlated positively with age (r=0.580, p=0.012), IDL-B correlated negatively with fasting insulin (r=–0.504, p=0.032), IR-HOMA (r=–0.498, p=0.035), AUC insulin (r=–0.519, p=0.027), and AAB insulin (r=–0.476, p=0.045); and positively with ISI Matsuda (r=0.470, p=0.048) (Figure 1). On the other hand, in controls, a positive correlation of systolic blood pressure with IDL-C, (r=0.518, p=0.023) and positive correlation of waist circumference with LDL1-2 subfraction (r=0.564, p=0.023) was found.

Correlations of HDL subfractions (L-HDL, I-HDL, and S-HDL) with anthropometric and cardiometabolic parameters did not reach statistical significance.

Discussion

In this study, we analyzed lipoprotein levels and their subfractions in newly diagnosed MS patients. Especially, the association of lipoprotein subfractions with insulin resistance and hyperinsulinemia, as it has been described in the literature (Lee et al. 2016), was investigated in this study.

In our previous study (Penesova et al. 2015), decreased insulin sensitivity and higher insulin response to oral glucose load has been found in newly diagnosed patients with MS. Since insulin resistance and hyperinsulinemia are the key features of the metabolic syndrome, we raised a question whether the insulin resistance and hyperinsulinemia might be associated with other features of the metabolic syndrome (obesity, hypertension, dyslipidemia).

Dyslipidemia in insulin resistance, assessed by conventional methods, is characterized by elevated triglycerides and low HDL cholesterol, whereas LDL cholesterol usually does not significantly differ from the insulin sensitive individuals (Garvey et al. 2003; Krauss 2004; Kassi et al. 2011). However, patients with insulin show typical resistance in predominance of small dense LDL particles (atherogenous), even if the absolute concentration of LDL cholesterol is not significantly altered (Haffner and ADA 2003).

Increased levels of total and HDL cholesterol in newly diagnosed MS patients when compared to healthy controls have been described (Giubilei et al. 2002). Our patients had slightly higher total cholesterol levels than controls, however, without reaching statistical significance (p=0.09). Significant positive correlation between the disease activity, expressed as a mean number of enhancing lesions of the MRI scans made in 6 consecutive months and both the total and LDL cholesterol levels has been described by Giubilei and co-workers (2002), who have suggested

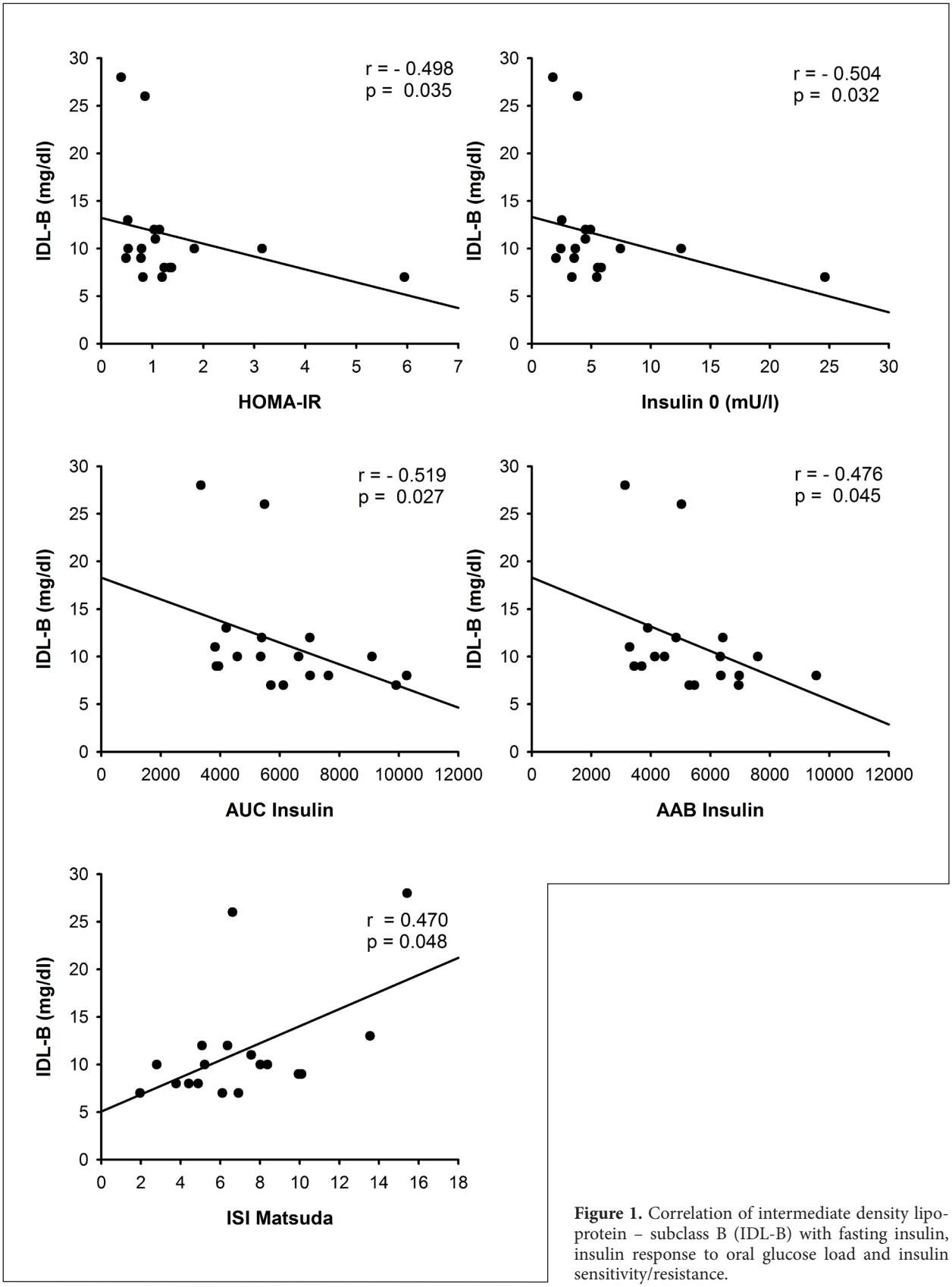

Figure 1. Correlation of intermediate density lipoprotein – subclass B (IDL-B) with fasting insulin, insulin response to oral glucose load and insulin sensitivity/resistance.

an early involvement of LDL in the development of MS lesions. Unfortunately, the above mentioned study did not involve evaluation of insulin resistance status. Similarly, several studies have demonstrated an altered lipid profile in a sense of a pre-cardiovascular-like lipoprotein profile in MS patients, such as increased LDL and total cholesterol levels, smaller LDL and HDL particle size, which was also associated with an increased disability progression in MS patients (Weinstock-Guttman et al. 2011; Mandoj et al. 2015; Jorissen et al. 2017; Jorissen et al. 2018). However, the duration of MS of these patients was more than 8–10 years in average.

Intermediate density lipoproteins (IDL) are atherogenic triglyceride rich remnants of VLDL, which are either cleared by the liver or converted further to LDL (Martin et al. 2015; Feingold and Grunfeld 2018). Several studies have proven a strong association of IDL with cardiovascular diseases, mainly coronary heart disease. They were also found to be predictive in the cardiovascular disease progression and an incident coronary heart disease (Krauss et al. 1987; Steiner et al. 1987; Nakamura et al. 2011; Ito et al. 2013; Joshi et al. 2016).

In the present study, noteworthy, we observed an inverse association between the level of IDL-B with fasting insulin, the insulin resistance estimated by HOMA-IR, insulin response expressed as AUC and AAB and positive association with insulin sensitivity estimated by ISI Matsuda in our group of MS patients. We believe that this may be considered as the first sign of changes in lipoprotein subclasses profile in relation to decreased insulin sensitivity and hyperinsulinemia in MS patients. Similar negative association of IDL-A and LDL1 with insulin resistance and abdominal obesity, suggesting a lesser influence on development of metabolic syndrome implying cardio-protective effect, has also been observed (Srisawasdi et al. 2015).

In our study, we did not found difference in the lipid profiles and lipoprotein subclasses between the newly diagnosed MS patients and controls. However, we found a negative association of IDL-B lipoprotein subfraction with the parameters of insulin resistance and hyperinsulinemia. Therefore, we conclude that insulin resistance precedes changes in lipid profile in the early stage of MS.

Acknowledgements

We express our appreciation to the multiple sclerosis patients and healthy volunteers who participated in the study. This study was supported by the grants: APVV-15-0228 (Slovak Research and Development Agency), VEGA 2/0161/16, VEGA 1/0109/16, VEGA 2/0072/18 and Era Net NEURON II.

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