ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. XXIII, N 2, 13 SECTIO DDD 2010

[1]Department of Laboratory Diagnostics,
[2]Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin

ELŻBIETA KIMAK[1], MAGDALENA HAŁABIŚ[1], JANUSZ SOLSKI[1], BOŻENA TARGOŃSKA-STĘPNIAK[2], MAGDALENA DRYGLEWSKA[2], MARIA MAJDAN[2]

Abnormal lipid and lipoprotein profiles in reumatoid arthritis

Nieprawidłowy profil lipidowy i lipoproteinowy w reumatoidalnym zapaleniu stawów

INTRODUCTION

Cardiovascular diseases are 1.5–2- fold more frequent in rheumatoid arthritis (RA) patients than in the general population [17]. High levels of LDL and VLDL are strongly associated with increased incidence of CAD, whereas HDL has a protective effect [1–5,11]. Although a number of disorders contributing to lipoprotein metabolism, such as those of the LDL receptor in familial hypercholesterolemia and cholesterol ester transfer protein deficiency in hyperalphalipoproteinemia, have been elucidated, they explain only a small fraction of the population variance of plasma lipoprotein levels [11]. Patients with rheumatoid arthritis frequently display an atherogenic lipid profile which is linked with inflammation. Tumor necrosis factor-alpha (TNF-alpha), a pivotal pro-inflammatory cytokine in RA may be involved in the development of the disturbed lipid metabolism and altered lipid and lipoprotein profiles observed in active RA [1–4,16–18]. Recently, studies strongly suggest that the disturbed lipoproteins and lipids metabolism is in part due to increased levels of oxidized lipids [13–16].

The aim of the studies was to investigate the concentration of lipid, lipoprotein (apoAI and apoB), lipid and lipoprotein ratios and ox-LDL levels in patients with active RA.

MATERIAL AND METHODS

The study group consisted of 10 patients (27–78 years) with RA. The control group was 13 subjects chosen from among apparently normolipidemic with normal blood tension healthy ones (aged from 22 to 52 years). The study was carried out in accordance with the guidelines of the Ethics Committee of the Medical University, Lublin.

Lipids, lipoproteins, routine laboratory parameters were obtained in serum after 14-hour overnight fasting. Blood was taken from veins into commercial tubes. Serum was immediately separated and

stored in aliquots at –80^{0}C until use. Lipids and lipoproteins (apoA, apoB) were determined on Hitachi 902 analyzer. Triglycerides (TG) were determined using the standard enzymatic technique (Roche kit). Total cholesterol (TC) was determined by the enzymatic-colorimetric methods (cholesterol CHOD-PAP, Roche), HDL-cholesterol (HDL-C) using the direct method with immunoinhibition, and LDL-cholesterol (LDL-C) was calculated according to the Friedewald formula [9]. Non-HDL-cholesterol (non-HDL-C) was calculated as total cholesterol (TC) minus HDL-C. ApoAI and apoB were measured using the turbidimetric methods (Roche kits). Enzyme immunoassay (ELISA) for the quantitative determination of human oxidized LDL (ox-LDL) in serum was used from Biomedica GmbH, Wien, Austria.

Statistical analysis was performed using one-way analysis of the student t-test for comparison in RA patients and the reference group. The data are expressed as means ± SD or median and min-max. The statistical significance of all variables was established at the level $p< 0.05$, and statistical analysis was performed using the STATISTICA program (Statsoft Polska, Krakow, Poland).

RESULTS

Table 1 presents the obtained results in RA patients, which shows that those had significantly increased TG, TC, LDL-C, non-HDL-C, apoB, ox-LDL concentrations and TG/HDL-C, TC/HDL-C, LDL-C/HDL-C ratios, and decreased HDL-C level and apoAI/apoB, HDL-C/apoAI ratios as compared to the reference group.

Table 1. Lipid and lipoprotein parameters and lipid and lipoprotein ratios in RA patients and the reference group

	RA patients n=10	Reference group n=13
TG mg/dl	132 ± 45**	87.68 ± 26.71
TC mg/dl	217 ± 38*	176.50 ± 28.03
LDL-C mg/dl	143 ± 32*	96. 92 ± 24.42
HDL-C mg/dl	45.0 ± 9.6*	57.71 ± 8.41
non-HDL-C mg/dl	169 ± 38.6*	113.29 ± 24.89
ApoA1 mg/dl	173 ± 30	163.1 ± 10.55
ApoB mg/dl	108 ± 26*	72.90 ± 15.63
ApoAI/apoB	1.60 ± 0.54**	2.24 ± 0.38
HDL-C/apoAI	0.26 ± 0.04***	0.35 ± 0.04
TC/HDL-C	5.03 ± 1.52***	2.96 ± 0.56
LDL-C/HDL-C	3.44 ± 1.22***	1.64 ± 0.47
TG/HDL-C	3.17 ± 1.60***	1.43 ± 0.50
Ox-LDL ng/ml	552(46-1010)***	115(35-153)

***p<0.001 **p<0.01 *p<0.05

DISCUSSION

The mortality gap between RA patients and the general population has been growing for several decades, largely because of excess CV deaths in patients with RA [5]. While research regarding this increased CV morbidity and mortality in RA has developed in recent years, a need remains for biomarkers to evaluate the effects of disease-modifying therapies and to identify high-risk patients for prevention strategies. Traditional coronary heart disease risk factors and Framingham risk guidelines alone are not sufficient to identify RA patients at high risk for coronary heart disease [5].

The findings of the study confirm these effects of inflammation on the various lipid concentrations. This is supported by the demonstration of a decrease in HDL-C level and an increase in triglycerides and apoB levels during an acute-phase response [4, 12, 20]. We found a higher concentration of lipids, especially TG, TC, LDL-C, non-HDL-C, apoB and TC/HDL-C, LDL-C/HDL-C, TG/HDL-C but the concentrations of HDL-C and apoAI/apoB and HDL-C/apoAI ratios were decreased. Corticosteroid use was associated with higher HDL-C and apoAI levels. Corticosteroids may raise HDL-C levels by increasing apoA-I production by the liver or/and via a mechanism decreasing CETP activity. Significantly reduced HDL-C levels and higher plasma CETP activity were observed after prednisone therapy [8, 10].

Several reports show anti-inflammatory effects of HDL and particularly apoAI. It was suggested that apoAI is able to inhibit interactions between T lymphocytes and monocytes, thereby modulating the inflammatory response [1]. Recently, it was suggested that tumor necrosis factor alfa (TNF-α) plays an important role in energy metabolism and is an effective lipid homeostasis regulator [6]. Moreover, another study showed the ability of apoAI to inhibit interleukin 1 and TNF-α, which further supports the theory of an active modulating role of lipids in inflammation [6, 7, 12–18]. The protective effect of HDL arises not only from its ability to promote cholesterol efflux from artery wall cell [5], but also from its anti-inflammatory properties, including its ability to protect low-density lipoprotein (LDL) against oxidation [13, 14, 19, 20]. However, proinflammatory HDL promoted, rather than prevented, the accumulation of oxidized phospholipids in LDL. Patients with proinflammatory HDL had abnormal protective capacity. Therefore, detection of proinflammatory HDL has also been identified as a useful marker for atherosclerosis [1, 5]. Oxidized low density lipoprotein can contribute to the development of atherosclerosis. Circulating ox-LDL and malondialdehyde-modified LDL have been reported to be useful markers for identifying coronary artery disease Wang [19, 20]. Moreover, ox-LDL lead to the formation of immune complexes in RA patients [19, 20].

CONCLUSIONS

Disturbances in lipid and lipoprotein profiles and high ox-LDL level suggest that RA patients have a high risk of arteriosclerosis. However, future studies are required.

REFERENCES

1. Ansell B.J., Navab M., Kamranpour N et al.: Inflammatory/anti-inflammatory properties of high-density lipoprotein distinguish patients from control subjects better than high-density lipoprotein cholesterol levels and are favorably affected by simvastatin treatment. Circulation, 108, 2751, 2003.

2. Allanore Y., Sellam J., Ekindjian O.G., Borderie D.: Effect of repeated infliximab therapy on serum lipid profile in patients with refractory rheumatoid arthritis. Clin. Chim. Acta, 365, 143, 2006.
3. Burger D., Dayer JM.: High-density lipoprotein-associated with apolipoprotein A-I: the missing link between infection and chronic inflammation? Autoimmun. Rev., 1, 111, 2002.
4. Cabana V.G., Siegel J.N., Sabesin S.M.: Effects of the acute phase response on the concentration and density distribution of plasma lipids and apolipoproteins. J. Lipid Res., 30, 39, 1989.
5. Charles-Schoeman C., Watanabe J., Lee Y.Y. et al.: Abnormal function of high-density lipoprotein is associated with poor disease control and an altered protein cargo in rheumatoid arthritis. Arthritis & Rheumatism, 60, 2870, 2009.
6. Chen X., Xun K., Chen L., Wang Y.: TNF-α, a potent lipid metabolism regulator. Cell Biochem. Funct., 27, 407, 2009.
7. Del Rincon I., Williams K., Stern M.P. et al.: Association between carotid atherosclerosis and markers of inflammation in rheumathoid arthritis patients and healthy subjects. Arthritis Reum., 48, 1833, 2003.
8. Donahoo W.T., Kosmiski L.A., Eckel RH.: Drugs causing dyslipoproteinemia. Endocrinol. Metab. Clin. North. Am., 27, 677, 1998.
9. Friedewald W.T., Levy R.I., Friedrickson D.S.: Estimation of the concentration of low-density lipoprotein cholesterol in plasma without the use of the preparative ultracentrifuge. Clin. Chem., 18, 499, 1972.
10. Garcia-Gomez C., Nolla J.M., Valverde J., et al.: Hihg HDL-cholesterol in women with rheumatoid arthritis on low-dose glucocorticoid therapy. Eur. J. Clin. Invest., 38, 686, 2008.
11. Gu L., Johnson M.W., Lius A.J.: Quantitative trait locus analysis of plasma lipoprotein levels in an autoimmune mouse model. Interactions between lipoprotein metabolism, autoimmune disease, and atherogenesis. Arterioscler. Thromb. Vasc. Biol., 19, 442, 1999.
12. Halm V.P, Nielen M.M.L, Nurmohamed M.T. et al.: Lipids and inflammation: serial measurements of the lipid profile of blood donors who later developed rheumatoid arthritis. Ann. Rheum. Dis., 66, 184, 2007.
13. Holvoet P., Mertens A., Verhamme P. et al.: Circulating oxidized LDL is a useful marker for identifying patients with coronary artery disease. Arterioscler. Thromb. Vasc. Biol., 21, 844, 2001.
14. Hulthe J., Fagerberg B.: Circulating oxidized LDL is associated with subclinical atherosclerosis development and inflammatory cytokines (AIR Study). Atheroscler. Thromb. Vasc. Biol., 22, 1162, 2002.
15. Hyka N., Dayer JM., Modoux C. et al.: Apolipopprotein AI inhibits the production of interleukin -1 beta and tumor necrosis factor-alpha by bloking contact-mediated activation of monocytes by T lymphocytes. Blood, 97, 2381, 2001.
16. Mc Mahon M., Brahn E.: Inflammatory lipids as a target for therapy in the rheumatic diseases. Expert Opin. Invest. Drugs, 17, 1213, 2008.
17. Popa C., Netea M.G., Van der Meer J.V.M. et al.: Modulation of lipoprotein plasma concentrations during long-term anti-TNF therapy in patients with active rheumatoid arthritis. Ann. Rheum. Dis., 66, 1503, 2007.
18. Seriolo B., Paolono S., Sulli A. et al.: Effects of anti-TNF-alpha treatment on lipid profile in patients with active rheumatoid arthritis. Ann. N.Y. Acad. Sci., 1069, 414, 2006.

19. Wang J., Hu B., Meng Y. et al.: The level of malondialdehyde-modified LDL and LDL immune complexes in patients with rheumatoid arthritis. Clin. Biochem., 42, 1352, 2009.
20. Watson A.D., Navab M., Hama S.Y. et al.: Effect of platelet activating factor-acetylhydrolase on the formation and action of minimally oxidized low density lipoprotein. J. Clin. Invest., 95, 774, 1995.

SUMMARY

Patients with rheumatoid arthritis (RA) have a high mortality rate than the general population with cardiovascular disease resulting from accelerated atherosclerosis being the most common cause of death. Plasma lipoprotein levels are an important determinant of atherosclerosis, the major cause of coronary artery disease (CAD) and stroke. The study group consisted of 10 patients (27–78 years) with RA. The reference group was made up of 13 healthy subjects (22–52 years). The aim of the present study was to investigate lipid, lipoprotein, ox-LDL concentrations and lipid and lipoprotein ratios in RA patients and compared to healthy subjects. The serum levels of lipids and apoAI, apoB, and oxidized-LDL (ox-LDL) were determined. Lipid and lipoprotein profiles were obtained in serum after 14-hour overnight fasting. Lipids and lipoproteins (apoA, apoB) were determined on Hitachi 902 analyzer. LDL-cholesterol (LDL-C) was calculated according to the Friedewald formula. Non-HDL-cholesterol (non-HDL-C) was calculated as total cholesterol (TC) minus HDL-C. Ox-LDL concentration was made using the ELISA method from BioMedica, Vien, Austria. The obtained results in RA patients show that those had significantly increased TG, TC, LDL-C, non-HDL-C, apoB, ox-LDL concentrations and TG/HDL-C, TC/HDL-C, LDL-C/HDL-C ratios, and decreased HDL-C level and apoAI/apoB, HDL-C/apoAI ratios as compared to the reference group. Conclusion. Disturbances in lipid and lipoprotein profiles and high ox-LDL level suggest that RA patients have a high risk of arteriosclerosis. However, future studies are required.

Key words: lipids, lipoproteins, oxidized LDL, rheumatoid arthritis

STRESZCZENIE

Pacjenci cierpiący na reumatoidalne zapalenie stawów wykazują wyższy odsetek zgonów z powodu choroby sercowo-naczyniowej wynikającej z przyspieszonej miażdżycy, niż notuje się to w ogólnej populacji. Poziomy osoczowych lipoprotein są przyczyną choroby naczyń wieńcowych, zawału i miażdżycy. Badana grupa liczyła 10 pacjentów (27–78 lat) z RA. Grupę referencyjną stanowiło 13 zdrowych osób (22–52 lata). Celem badań było badanie stężeń lipidów, lipoprotein, ox-LDL i wskaźników lipidowych oraz lipoproteinowych u pacjentów z RA i porównanie z grupą osób zdrowych. Profil lipidowy i lipoproteinowy oznaczono w surowicy pacjentów po 14-godz. głodzeniu. Lipidy i lipoproteidy (apoAI, apoB) były oznaczone na analizatorze Hitachi 902. LDL-cholesterol wyliczono z wzoru Friedewalda. Cholesterol zawarty poza frakcją HDL (non-HDL-C) wyliczono z różnicy całkowitego cholesterolu i HDL-C. Stężenie ox-LDL było oznaczone przy użyciu testu ELISA firmy BioMedica, Wiedeń, Austria. Otrzymane wyniki pacjentów cierpiących na RA wykazały, że chorzy mają istotnie podwyższone stężenie TC, TG, LDL-C, non-HDL-C, apoB, ox-LDL i wskaźniki TG/HDL-C, TC/HDL-C, LDL-C/HDL-C oraz obniżone stężenie HDL-C

i wartości wskaźników apoAI/apoB, HDL-C/apoAI w porównaniu z grupą referencyjną. Zaburzenia w profilu lipidowym i lipoproteinowym oraz wysokie stężenie ox-LDL sugerują podwyższone ryzyko miażdżycy pacjentów cierpiących na RA. Jednakże wymagane są dalsze badania.

Słowa kluczowe: lipidy, lipoproteiny, ultlenione LDL, reumatoidalne zapalenie stawów.