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Newly Diagnosed Patients with Type 2 Diabetes Mellitus Reveal Different Lipid Pattern

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SUMMARY

Patients with type 2 diabetes mellitus are having the typical form of atherogenic dyslipidemia. This dyslipidaemia type is typically present with the increase of triglyceride levels, de-crease of HDL-cholesterol and small increase of LDL-cholesterol levels (predominantly with small dense LDL-particles). The prognostic importance of this type of atherogenic dyslipidae-mia is of the increase of the risk of atherothrombosis.

Estimation of the size of lipoprotein particles among newly diagnosed, untreated patients with type 2 diabetes mellitus have not been evaluated yet. Dyslipidaemia among these patients has its course and it changes after the treatment. At the early beginning it is characterized by the significant increase of VLDL, large and middle size IDL lipoprotein particles, as well as by lowering of HDL particles. This lipoprotein profile has its own atherogenic potential. The course of the disease later leads to the typical known change of dyslipidaemia, characterized as atherogenic dyslipidemia (increased LDL-cholesterol and triglycerides with the persis-tence of the decreased HDL-cholesterol).

Hypolipidemic treatment leads to the significant lowering of the cardiovascular risk, however despite treatment with statin or fibrate residual cardiovascular risk remains still very high.

Keywords: Diabetes Mellitus; Dyslipoproteinaemias; Residual Cardiovascular Risk

INTRODUCTION

Among patients with type 2 diabetes mellitus, as well as with present insulin resistence there is the cluster of lipoproteine spectrum abnormalities present. Dyslipidemia contributes to the very high residual cardiovascular risk presence among these patients [1]. It enhances athero-thrombosis and leads to the coronary heart disease equivalent [2]. This lipid spectrum contains low HDL-cholesterol levels, high triglycerids, often with nearly normal LDL-cho- lesterolu, but with predominant presence of small-dense LDL particles [3]. Present insulín resistence has its influence on the lipoprotein sizes and subtype of concentrations of other par- ticles (VLDL, LDL and HDL [4,5]. This lipid change leads to the increased cardiovascular risk also among the patients with type 2 diabetes mellitus. [6,7]. Similarly association is pre-sent among lipoprotein particle size and density and development of coronary heart disease [8,9]. The most predictive value represent the small dense lipid particles, nowadays described as the independent negative prognostic factor, the atherogenic dyslipidemia type [10,11]. For the proper lipoprotein particle measurements Lipoprotein Quantimetrics method was appro-ved by FDA for the clinical practice in the biological systems [12,13].

MATERIALS AND METHODS

30 consecutive newly diagnosed and untreated type 2 diabetes mellitus patients, sent to the diabetic centre clinic from the primare care physicians were followed-up. Their characteristics are presented in the **Table 1**. It was compared with the controls of sample match clinically healthy, asymptomatic persons. All of them have signed the informed consent for the follow-up study, approved by the central ethical committee. Lipoprotein particle size were measured with Lipoprint LDL Quantimetrics method, which enables to discriminate LDL 1-3, IDL 1-3, VLDL and HDL [13,14]. Statistical analysis data are given as the mean ± standard errors. Normal distribution of variables was controlled by Kolmogorov-Smirnov´s test, mean levels between the samples were compared using Mann-Whitney´s test, as its values had not normal distribution.

Table 1: Characteristics of the followed-up type 2 diabetes mellitus patients.

Sex: males: 11
Females: 19
age: 55,6 +- 5,5 yrs (SD)
BMI: 32,63 +- 4,95
BPs: 133,13 +- 12,65 mmHg
BPd: 82,04 +- 7,6 mmHg
creatinine (s): 73,0 +- 17,54
acid uric: 335,4 +- 67,88 μmol/l
ALT: 0,58 +- 0,27 μkat/l
Total cholesterol: 5,50 +- 1,8 mmol/l
Triglycerides: 1,99 +- 1,24 mmol/l
C-peptide: 2,74 +- 1,0 mmol/l
hsCRP: 5,1 +- 3,31

RESULTS

Lipoprint analysis revealed, that dyslipidemia type among newly diagnosed and untreated type 2 diabetes mellitus patients differ from the type described as the typical atherogenic dyslipidemia. These findings ares presented in the **Table 2.** However the constant finding is the significant lowering of HDL cholesterol. This characteristic feature remains during the course of the disease. LDL cholesterol is changing during longer lasting type 2 diabetes mellitus. It differs from the comorbidities and initiation of the treatment. There is later appearence of the LDL increase, particularly small dense LDL particles. At the beginning of the diagnostics of these patients mainly VLAD and large and middle IDL lipoproteins are dominating. Despite other lipid type appearence, these lipoproteins are carrying the certain atherogenic potential, con-tributing to the increased atherothrombotic and cardiovascular risk.

Table 2: Lipids (mg/dl) and lipoprotein sizes at the time of first manifestation of type 2 diabetes mellitus patients.

	DM 2 (n=30)	controls (n=30)	p value	statistical significance
VLDL	30.55 ± 11.16	23.06 ± 8.505	<0.05	*
large IDL	25,97 ± 7.599	21.75 ± 5.745	<0.05	*
medium IDL	13.72 ± 5.861	8.750 ± 2.864	<0.001	**
small IDL	21.52 ± 9.144	19.38 ± 10.65	>0.05	ns
LDL	126.6 ± 42.22	104.2 ± 34.76	>0.05	ns
LDL-1	46.52 ± 16.33	37.88 ± 10.46	>0.05	ns
LDL-2	18.59 ± 12.87	16.06 ± 15.47	>0.05	ns
LDL-3	1.586 ± 3.831	1.625 ± 1.14	>0.05	ns
HDL	48.66 ± 12.21	58.00 ± 11.11	<0.05	*

VLDL = very low density lipoproteins
IDL = intermediate density lipoproteins
LDL = low density lipoproteins
HDL = high density lipoproteins
ns = non significant

DISCUSSION

Pathophysiology of atherogenic dyslipidemia is characterised by the lipoprotein changes rich of triglycerids. These changes are connected with the VLDL increase from the liver as well as impaired clearence and chylomicrons from the intestine. Of importance there is prolonged re-tention of VLDL and postprandial chylomicrons, partially lipolysed particle remnants. These include also IDL and in men they are also significant atherogenic particles [15]. Both of these mechanisms, increased creation and concommitant longer clearence of large VLDL plasma particles lead to the increase of precursors of small dense LDL particles [16]. With the development of new laboratory examining methods seven LDL subfractions were identified. They differ in their metabolism and pathophysiology and also in atherogenic potential [16,17]. VLDL plasmatic levels correlate with increased density and decreased particle size of LDL [18,19]. The size and desity of LDL particles correlate with the plasmatic HDL particle levels, predominantly HDL2 [20]. Decreased HDL cholesterol levels among type 2 diabetes mellitus patients is caused by the increased transport of cholesterol from HDL into triglyce-ride rich lipoproteins and reciprocal transport of triglycerides into HDL. Triglyceride rich HDL particles are hydrolysed by hepatic lipase and are rapidly catabolised and released from the plasma [21]. An important lipid abnormality is the increase of free fatty acids, present among these patients even before hyperglycaemia appearence [22]. There is also an increased efflux of free fatty acids from the

fatty tissue and their impaired uptake of the sceletal muscles insulin mediated [23]. Inzuline resistence increase the hepatic lipase activity, responsible for phospholipid hydrolysis in LDL and HDL particles and leads to the increase of small dense LDL particles and decrease of the HDL2 [24]. Relationship between the low HDL, small dense LDL particles and increased triglycerids to cardiovascular risk is therefore well known. Therefore is included into the important measures of the secondary prevention [25].

CONCLUSIONS

Untreated, newly diagnosed type 2 diabetes mellitus patients reveal the whole cluster of lipid and lipoprotein abnormalities. They are connected to the VLDL particle changes and to the enhanced process of atherothrombosis. Atherothrombotic risk is the sum of all lipid factors: low HDL-cholesterol, presence of small dense LDL-cholesterol particles and high triglycerides. All parts of this cluster bring their particular risk also independently. Atherogenic dyslipidemia is present already at the time of the first manifestation of diabetes mellitus. Therefore nonpharmacologic (diet, exercise, weight control, smoking cessation) as well as pharmacologic treatment (statins) should be introduced among these patient in order to lower their high cardiovasculkar risk. Despite treatment still high residual cardiovascular risk is present among this patient group.

References

1. Haffner SM, Mykkänen L, Festa A, Burke JP, Stern MP. Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects: implications for preventing coronary heart disease during the prediabetic state. Circulation. 2000; 101: 975-980.
2. Haffner SM,Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals do the clock for coronary heart disease start ticking before the onset of clinical diabetes? JAMA 1990: 263: 2893-2898.
3. Krauss RM. Lipids and lipoproteins in patients with type 2 diabetes. Diabetes Care. 2004; 27: 1496-1504.
4. Reaven GM, Chen YD, Jeppesen J, Maheux P, Krauss RM. Insulin resistance and hyperinsulinemia in individuals with small, dense low density lipoprotein particles. J Clin Invest. 1993; 92: 141-146.
5. Garvey WT, Kwon S, Zheng D, Shaughnessy S, Wallace P, et al. Effects of insulin resistance and type 2 diabetes on lipoprotein subclass particle size and concentration determined by nuclear magnetic resonance. Diabetes. 2003; 52: 453-462.
6. Lamarche B, Tchernof A, Moorjani S, Cantin B, Dagenais GR, Lupien PJ, Després JP. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men. Prospective results from the Québec Cardiovascular Study. Circulation. 1997; 95: 69-75.
7. Gardner CD, Fortmann SP, Krauss RM. Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. JAMA. 1996; 276: 875-881.
8. Campos H, Genest JJ, Blijlevens E, McNamara JR, Jenner JL, et al. Low density lipoprotein particle size and coronary artery disease. Arterioscler Thromb. 1992; 12: 187-195.
9. Austin MA, Breslow JL, Hennekens CH, Buring JE, Willett WC, et al. Low-density lipoprotein subclass patterns and risk of myocardial infarction. JAMA. 1988; 260: 1917-1921.
10. Coresh J, Kwiterovich PO, Smith HH, Bachorik PS. Association of plasma triglyceride concentration and LDL particle diameter, density, and chemical composition with premature coronary artery disease in men and women. J Lipid Res. 1993; 34: 1687-1697.
11. Crouse JR, Parks JS, Schey HM, Kahl FR. Studies of low density lipoprotein molecular weight in human beings with coronary artery disease. J Lipid Res. 1985; 26: 566-574.
12. Austin MA, King MC, Vranizan KM, Krauss RM. Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk. Circulation. 1990; 82: 495-506.

13. Oravec S, Dostal E, Dukát A, Gavorník P, Kucera M, Gruber K. HDL subfractions analysis: a new laboratory diagnostic assay for patients with cardiovascular diseases and dyslipoproteinemia. Neuro Endocrinol Lett. 2011; 32: 502-509.

14. DukÃ¡t A, FÃ¡bryovÃ¡ L, Oravec S, Sabaka P, MistrÃkovÃ¡ L, BalÃ¡Å¾ D, Gavornik P. [Lipids and the size of lipoprotein particles in newly diagnosed and untreated patients with type 2 diabetes mellitus]. Vnitr Lek. 2013; 59: 450-452.

15. Krauss RM. Atherogenicity of triglyceride-rich lipoproteins. Am J Cardiol. 1998; 81: 13B-17B.

16. Berneis KK, Krauss RM. Metabolic origins and clinical significance of LDL heterogeneity. J Lipid Res. 2002; 43: 1363-1379.

17. Goliasch G, Oravec S, Blessberger H, Dostal E, Hoke M, et al. Relative importance of different lipid risk factors for the development of myocardial infarction at a very young age (â‰¤ 40 years of age). Eur J Clin Invest. 2012; 42: 631-636.

18. McNamara JR, Campos H, Ordovas JM, Peterson J, Wilson PW, et al. Effect of gender, age, and lipid status on low density lipoprotein subfraction distribution. Results from the Framingham Offspring Study. Arteriosclerosis. 1987; 7: 483-490.

19. McNamara JR, Jenner JL, Li Z, Wilson PW, Schaefer EJ. Change in LDL particle size is associated with change in plasma triglyceride concentration. Arterioscler Thromb. 1992; 12: 1284-1290.

20. Krauss RM, Williams PT, Lindgren FT, Wood PD. Coordinate changes in levels of human serum low and high density lipoprotein subclasses in healthy men. Arteriosclerosis. 1988; 8: 155-162.

21. Hopkins GJ, Barter PJ. Role of triglyceride-rich lipoproteins and hepatic lipase in determining the particle size and composition of high density lipoproteins. J Lipid Res. 1986; 27: 1265-1277.

22. Boden G. Role of fatty acids in the pathogenesis of insulin resistance and NIDDM. Diabetes. 1997; 46: 3-10.

23. Kelley DE, Simoneau JA. Impaired free fatty acid utilization by skeletal muscle in non-insulin-dependent diabetes mellitus. J Clin Invest. 1994; 94: 2349-2356.

24. Zambon A, Austin MA, Brown BG, Hokanson JE, Brunzell JD. Effect of hepatic lipase on LDL in normal men and those with coronary artery disease. Arterioscler Thromb. 1993; 13: 147-153.

25. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012; 33: 1635-1701.