BIOPHYSICS AND BIOCHEMISTRY

Interrelation between Malonyl Dialdehyde-Dependent Modification and Cholesterol Content in Low-Density Lipoproteins

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Epidemiological study of an independent representative sample of population revealed a strong positive correlation between the content of oxidized (MDA-modified) LDL and concentration of atherosclerosis biomarkers (total cholesterol and LDL cholesterol) in blood plasma from 348 probands. The correlation between these parameters was more significant in atherosclerotic patients, but was less pronounced in probands with diabetes mellitus. The correlation between the concentration of atherosclerosis markers and content of MDA was absent in probands with diabetes mellitus. These data attest to the presence of LDL-modifying agents differing from MDA (*e.g.*, glyoxal and methylglyoxal) in the blood of diabetes mellitus patients. We conclude that the content of MDA-modified LDL can serve as an additional biomarker of atherosclerosis.

Key Words: *carbonyl compounds; modified low-density lipoproteins; biomarkers of atherosclerosis; diabetes mellitus*

Progressive atherosclerosis is accompanied by the development of oxidative stress and increase in free radical oxidation of LDL. Lipid hydroperoxides of LDL undergo oxidative destruction, which results in the formation of low-molecular-weight carbonyl compounds (*e.g.*, MDA). They are capable of inducing modification of LDL apoprotein B-100 [2,3]. Accumulation of MDA-modified LDL in the vascular wall is accompanied by pre-atherogenic injury [2,3]. These data suggest that the content of oxidized (MDA-modified) LDL in blood plasma can serve as a biomarker of atherosclerosis. This work describes the results of an epidemiological study comparing the concentrations of total cholesterol (CH) and LDL CH (known biomarkers of atherosclerosis) with the content of oxidized LDL in blood plasma from probands.

MATERIALS AND METHODS

We analyzed blood plasma samples obtained during an epidemiological survey of an independent representative sample of probands from Tallinn's population (20-64-year-old men) within the framework of CINDI program. Arterial hypertension, type 2 diabetes mellitus, and postinfarction cardiosclerosis were re-

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vealed during clinical examination. The excess-weight group consisted of patients with Quetelet index >25. The smoker group consisted of patients who smoked at least two cigarettes a day for the past year. The concentrations of total CH, LDL CH, and glucose in blood plasma were measured on a Roche Cobas 6000 analyzer with Roche Diagnostics kits (Mannheim). MDA content in blood plasma was estimated from the amount of TBA-reactive products in the supernatant after precipitation with trichloroacetic acid [4]. The concentration of oxidized (MDA-modified) LDL was measured immunochemically on a BioTek EL 808 plate spectrophotometer with Mercodia kits [10]. Hemoglobin concentration in the erythrocyte lysate was evaluated by the hemoglobin cyanide method with Herbos Dijagnostica kits. The reagents were manufactured by Sigma Chemicals.

The results were analyzed by StatSoft Inc. software (Statistica 6.0).

RESULTS

A strong positive correlation (r=0.90; p<0.05) was found between the known markers of atherosclerosis. The degree of hypercholesterolemia (total CH concentration) correlated with LDL CH content in blood plasma from 348 probands. Table 1 shows the concentration of MDA-modified LDL in probands with different risk factors of atherosclerosis (*e.g.*, hypercholesterolemia and hypertriglyceridemia). The content of MDA-modified LDL was elevated by 33% in hypercholesterolemic patients, but remained practically unchanged in probands with hypertriglyceridemia (Table 1). These data are consistent with the results of our previous experiments demonstrating the important role

TABLE 1. Content of Oxidized (MDA-Modified) LDL in the Blood from Probands with Hypercholesterolemia and Hypertriglyceridemia

Probands	Content of MDA-modified LDL, U/liter blood plasma
Without hypercholesterolemia (n=131)	56.8±14.6
With hypercholesterolemia (n=217)	75.4±16.3*
Without hypertriglyceridemia (n=281)	67.9±18.0
With hypertriglyceridemia (n=67)	70.5±17.8+

Note. *p<0.01 compared to patients without hypercholesterolemia; +p=0.28 compared to patients without hypertriglyceridemia.

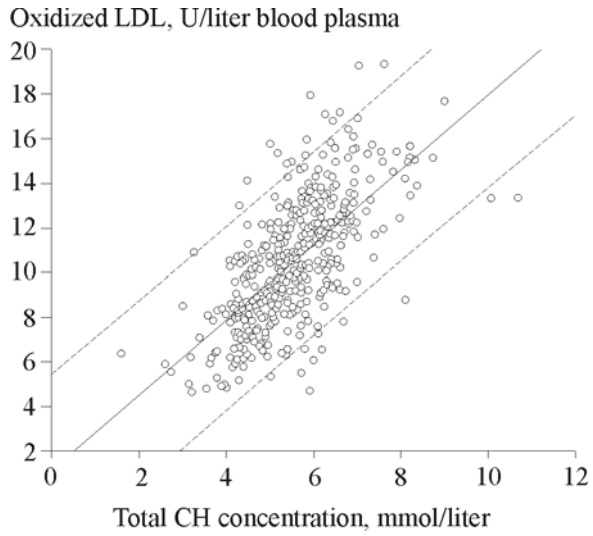

Fig. 1. Correlation between the concentrations of oxidized LDL and total CH in the studied population (r=0.68; p<0.05).

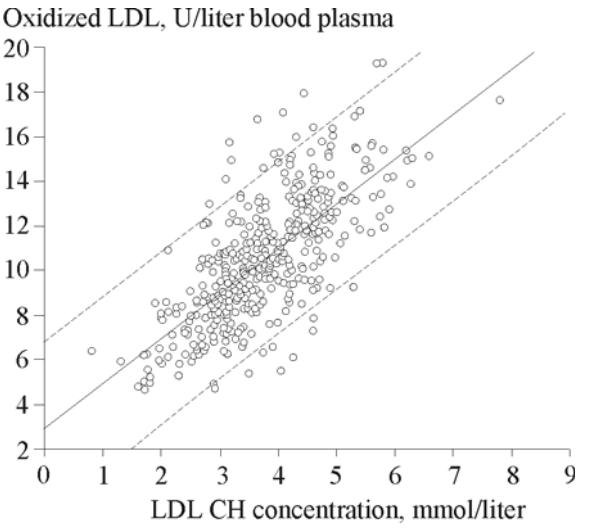

Fig. 2. Correlation between the concentrations of oxidized LDL and LDL CH in the studied population (r=0.72; p<0.05).

of LDL peroxidation in the pathogenesis of atherosclerosis and confirm the assumption that disturbances in lipid metabolism during atherogenesis can contribute to activation of free radical processes [1,2].

Published data suggest the existence of interrelations between atherosclerosis and elevated content of MDA-modified LDL in blood plasma [6,7,10,11]. Our study revealed a strong positive correlation between the concentration of total CH or LDL CH and content of oxidized (MDA-modified) LDL in blood plasma from probands (r=0.68 and 0.72, respectively; p<0.05; Figs. 1 and 2). The greater is the atherogenicity of LDL (elevated content of CH), the higher is the degree of LDL oxidation (strong modification of LDL with MDA). The correlation between the concentration of total CH or LDL CH and content of MDA-modified

LDL was more significant in patients with postinfarction cardiosclerosis (r=0.82 and 0.83, respectively; p<0.05). By contrast, the correlation between atherosclerosis biomarkers (concentrations of total CH and LDL CH) and content of MDA-modified LDL was less pronounced in patients with type 2 diabetes mellitus (r=0.57 and 0.64, respectively; p<0.05). No correlation was found between biomarkers of atherosclerosis and stationary concentration of MDA (TBA-reactive products) in blood plasma from probands with diabetes mellitus (r=0.25 and 0.05, respectively; p>0.05). The blood of diabetes mellitus patients probably accumulates carbonyl compound-modified LDL (*e.g.*, glyoxal and methylglyoxal), but not MDA-modified LDL [2,3]. Our findings indicate that antigenic properties of MDA-modified apoprotein B-100 in LDL differ from those of glyoxal-modified and methylglyoxal-modified apoproteins B [3]. We conclude that the content of oxidized (MDA-modified) LDL can serve as an additional biomarker of atherosclerosis. Clinical evaluation of oxidized (MDA-modified) LDL can be used as a more specific and sensitive method than the assay of other biomarkers of atherosclerosis (*e.g.*, total CH and LDL CH).

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