Review Article

MODIFIED LIPOPROTEINS IN ATHEROSCLEROSIS AND DIABETES

(Received 11 October, 1997)

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ABSTRACT

In atherosclerosis and diabetes functional and structural changes of lipoproteins occur as a result of peroxidation and glycation. LDL is the most modified fraction among the lipoproteins. Oxidation of LDL which probably occurs in subendotelial space is associated with the lipid peroxidation of PUFAs forming lipid hydroperoxides and fragmentation of apoB. As a result oxidized LDL has a different characteristic in electrophoresis and has less PUFA more aldehydes, more lysophosphatidylcholine in the lipid phase and degraded apoB. The alterations lead to some functional changes in LDL. Oxidation causes some cytotoxic effects in the cells. Increased monocyte binding, inhibition of endothelial derived factor (EDRF), increased expression of endotelin mRNA, induction of PGI2 synthesis from endothelial cells are some of the oxidized LDL related changes of the cells. Antibodies against oxidized LDL are also found in atherosclerotic patients and suggest that it is important in the atherogenic effect of LDL. Glycation is another change in the structure of LDL in diabetes resulting from the increased glucose concentration. In vivo glycation is linked with oxidation. Autoxidation of glucose and Amadori rearrangement products causing lipid peroxidation and forming superoxide radicals or decreased clearance of glycated proteins are the possible mechanisms.

INTRODUCTION

Coronary heart disease (CHD) as a result of atherosclerosis is a major cause of morbidity and mortality in the developed world and is also the major cause of death in subjects with diabetes mellitus.

Increased low density lipoprotein (LDL) cholesterol concentration is a well-established risk factor for CHD. The incorporation of modified LDL into an atheromatous plaque with the macrophage scavenger receptor is also established very well. In atherosclerosis and diabetes structural and functional changes in lipoproteins were detected by in vivo and in vitro studies. The formation of these changes are mainly achieved by oxidation and glycation (1).

It is believed that peroxidation reactions are important in the pathogenesis of atherosclerosis, cancer and aging (2).

Lipid peroxidation is a complex process with unpaired electrons, free radicals or oxidized species formed by the interaction of free radicals with lipids that are responsible from these reactions (2). The reactions generally initiate with the deletion of a hydrogen atom from unsaturated fatty acid and result with the formation of lipid radicals. It is associated with the rearrangement of the double bonds in unsaturated lipids and destruction of membrane lipids which breakdown products such as alcohols, ketones, aldehydes and ethers are produced (3) and also the disruption of membrane integrity happens (2,3). It is suggested that the disruption of the membrane integrity is the cause of the decrease in glucose 6-phosphatase activity during the NADPH-dependent lipid peroxidation (3).

Biological membranes (3) and all the lipoprotein fractions are susceptible to oxidation in different rates because of the ester cholesterol and polyunsaturated fatty acid (PUFA) contents of phospholipids (4). Most of the reports on atherosclerosis are concerned about LDL because atherosclerosis is mainly associated with LDL and in vivo LDL glycation can be mimicked by in vitro LDL glycation (5).

STRUCTURE OF LDL

The core of LDL particle consists of ester cholesterol and triglycerides and is surrounded with the phospholipid monolayer with PUFAs and free cholesterol (6). ApoB is embedded in the outer monolayer. The main PUFA is linoleic acid but less amount of arachidonic acid and docosahexaenoic acid are also present (4,7). The PUFAs are protected from the free radical attacks by lyphophilic antioxidants (7). α-tocopherol which is the most

relevant antioxidant maintains 30% of the resistance to oxidation. A LDL particle contains roughly seven molecules of α-tocopherol (4,7). The other substances with potential antioxidant activity are γ-tocopherol, carotenoids and ubiquinol (7). Tocopherols are located in the phospholipid layer of lipoproteins and β-carotene in the lipid core (4). PUFA and antioxidant content of LDL particles differ among individuals. The ratio of antioxidants to PUFA is roughly 1:170 (7).

OXIDATION OF LDL

The mechanism of in vivo oxidation is still obscure and can be related to many factors. The oxidation of LDL probably occurs in the subendothelial space, not in plasma where there is a high protective effect of antioxidants (5).

LDL can be oxidized by acetylation, metal ions as Cu^{2+}, malondialdehyde or interaction with endothelial cells (1). In principle the oxidation of LDL by cells or a cell-free system is the lipid peroxidation of PUFAs in LDL by the free radical chain reaction forming lipid hydroperoxides (7). Fe and Cu help in the degradation of the peroxides ions which are already found in LDL and this maintains the advanced peroxidation of PUFAs (4).

In the presence of hydrogen peroxide (H_2O_2), proteins containing heme undergo oxidation, producing ferril and ferril radicals. These radicals and the met form of the hemoproteins oxidize LDL. Nitric oxide (NO) also undergoes a reaction with the heme containing proteins and enhances the oxidation of LDL by metmyoglobin in the presence of excess H_2O_2 (4).

The oxidation of LDL occurs in three phases. The characteristics of the LDL oxidation are as follows: disappearance of the antioxidants in the lag phase; increase of hydroperoxide and conjugated diens in the propagation phase; the production of degradation products and changes in the LDL particle in the decomposition phase (7).

Primarily the lipid peroxidation of unsaturated fatty acids occurs in the oxidative modification of lipoproteins (5,7). The production of lipid peroxides results with the change in the absorbance at 234 nm that indicates the formation of conjugated diens (5). Lipid hydroperoxides degrade to reactive aldehydes such as malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), hexanal (5,7). In addition some other reactions such as the formation of lysolecithin, oxidation of cholesterol moiety may also occur (7). Several investigators showed; the covalent binding of lipid peroxidation products (such as aldehydes) to the amino acid remnants (e.g E-amino group of lysine) of apoB; the apoB fragmentation induced by free radicals and the formation of high molecular weight aggregates. These result with the formation of a modified apoB which cannot be recognized by B/E receptors but by the scavenger receptors of macrophages (5,7). As a result of this apoB modification, an increase in the electronegative charge of the apolipoprotein occurs which changes the eletrophoretic mobility of LDL (1,8) and these oxidized LDLs run faster than native LDL (5,7).

As a consequence the oxidized LDL has; a) higher density, greater anodic mobility on agarose gel electrophoresis, reduction in ester cholesterol (8) b) decreased amount of PUFA and increased aldehyde in the lipid phase (9) c) degradation of apoB d) induced phospholipase A2 activity which results with the increase in lysophosphatidylcholine (Lyso-Pc) (10). Besides this these LDLs differ in size and have a tendency to aggregate (1).

There is a weak correlation between the level of endogenous α-tochopherol isolated from LDL and susceptibility to oxidation (4) and between the α-tochopherol or total antioxidants and lag phase (6,11). However, the addition of α-tochopherol or intake of high dosage of vitamin E prolongs the lag phase. Because the monounsaturated fatty acids are less susceptible to oxidation, enrichment of diet by monounaturated fatty acids (oleic acid) also prolongs the lag phase (4).

FORMATION OF ATHEROSCLEROTIC PLAQUE

It is still obscure how the formation of atherosclerotic plaques initiated but it is supposed to be related with the endothelial injury that results with a series of events. This includes the expression of adhesion molecules on the luminal surfaces of the cells. The adhesion of monocytes to endothelia is one of the early processes. These monocytes migrate to the endothelial junctions where they transform to macrophages. Early atherosclerotic plaques are characterized by a significant increase in macrophages. These cells can uptake more lipid, and this leads to the formation of foam cells that carry most of the intracellular lipid in the atherosclerotic plaques. Another important event in the early stage of atherosclerosis is the proliferation of the cells especially smooth muscle cells that break through the elastic lamina and form the main mass of the atherosclerotic plaque. Smooth muscle cells de-differentiate during the proliferation and can uptake lipid and form the foam cells. The structure of the atherosclerotic plaques may show variation in their contents; some contain a high amount of lipid and macrophages while the others contain less lipid and more fibrous material and connective tissue that is

derived from the proliferation of smooth muscle cells. It is proposed that plaques rich in macrophages have weak mechanic characteristics and a tendency to form fissure that leads to thrombosis accompanied by infarction (4).

Regulation of vascular tonus and antithrombotic characteristics which are among the functions of endothelia are important in cardiovascular disease. Endothelium derived relaxation factor (EDRF) (nitric oxide) and prostacyclin are released by vascular endothelia. Both inhibit the platelet aggregation and evoke vasodilatation in smooth muscle cells (4).

ALTERED FUNCTIONS OF OXIDIZED LDL

Alterations in chemical and structural composition of lipoproteins result with some functional changes (1).

The important points are the role of oLDL in the accumulation of monocyte macrophages in the arterial wall, the formation of foam cells as a consequence of uncontrolled uptake of oLDL by the macrophage scavenger receptors, the cytotoxicity and the immunologic properties of oLDL (11,12).

The effect of lipoprotein oxidation products is the direct cytotoxic effect which leads to the impairment of the cell function (4). The cytotoxic effect of oxidized LDL is probably due to the lipid peroxidation products such as HNE, 2-alkenals, 2,34-alkadienals and the oxidized form of cholesterol (5,7). Beside this, especially mild oxidation has an effect on the transcription of special proteins that enhances the expression of these special proteins which is important in the cell function. The exposure of endothelia to the minimally oxidized LDL results with the four folds enhanced monocyte binding, and which indicates the potential effect of oxidation in the early stage of atherosclerosis (4). Because the oxidized LDLs cause ester cholesterol deposition in the mononuclear phagocytic system cells they are accepted to posses an atherogenic potential (1). Oxidized LDL also induces in vitro collagen formation in smooth muscle cells (4).

Oxidized LDL can inhibit the activity of EDRF significantly. In coronary arteries of hypercholesterolemic patients, with the dysfunction of receptor-mediated relaxation the endothelium dependent relaxation is impaired progressively. In some arteries it leads to the complete loss of endothelium dependent relaxation. The degree and reversibility of this inhibition is affected by the exposure of native LDL to oxidation (4).

Some authors showed that in diet induced hypercholesterolemia there is a focal loss of endothelial cells or shortened platelet half life. The secretion of prostacyclin is induced by the presence of HDL or LDL. Oxidized LDL induces the synthesis of PGI2 from endothelial cells more than native LDL. However, if the exposure to oxidized LDL is prolonged PGI2 synthesis may be diminished (4).

Enhanced sensitization in atherosclerotic vessels to endotelin which is a vasoconstrictor peptide is detected. The expression of endothelin mRNA is enhanced by oxidized LDL (4). Oxidized LDL affects the production of cytokines and growth factors by macrophages and vascular cells, the expression of cell adhesion molecules and the cell mobility. It is shown that oxidized LDL inhibits the production of platelet-derived growth factor (PDGF) by the endothelial cells and macrophages, and supresses the gene expression of tumor necrose factor-α (TNF-α), interleukin 1 α (IL-1 α) and monocyte chemotactic protein (MCP-1) in macrophages (5).

It is reported that LDL and HDL inhibit thromboplastin activity in vitro, but this effect is reversed when LDL is oxidized and oxidized lipoproteins stimulate the thromboplastin induced coagulation (4). It is also shown that oxidized LDL affects fibrinolysis by stimulating plasminogen activator inhibitor 1 PAI-I (4,13) and inhibiting secretion of tissue plasminogen activator (tPA) from endothelial cells (13,14).

LDL also has a direct effect on platelets possibly by a receptor mediated mechanism. Cu^{2+} oxidized LDL sensitizes the platelets more effectively than native LDL (4). Oxidized LDL inhibits protein C synthesis (15).

It is obvious that in the development of atherosclerosis, LDL is transformed to an atherogenic particle by oxidation that enhances the presence of macrophages on vessel wall and accumulation of lipids in macrophages and forming a necrotic core (2). The transformation of macrophages to foam cells can be attributed to the rapid and unregulated uptake of LDL by these macrophages (12).

LDL AND IMMUNOPATHOGENESIS

Antibodies against oxidized LDL which are also found naturally in humans are detected in higher proportion in atherosclerotic patients having inflammatory reaction to the atherosclerotic plaques (5). It is also reported that there is a strong relation between the autoantibodies aganist ox-LDL and progression of carotid atherosclerosis (16).
Beside this immune complexes containing lipoprotein are also detected in coronary artery disease. In vitro LDL/antiLDL immune complexes (LDL-IC) are shown to be the potent inducers of foam cell formation (5). LDL-IC is taken up by macrophages via the

interaction of two receptors: One is Fcγ receptor which internalizes the larger part of the LDL-IC and the second is the classical LDL receptor (17). Another effect of immune complexes is the activation of macrophages. Effects of monocyte/macrophages' activation are various. Among the biological active mediators of stimulated monocyte/macrophages are the growth factors as PDGF-BB, cytokines as TNF-α, IL-1, PGE2, α-interferon, protease, collagenase and oxygen radicals. Secretion of TNF-α and IL-1 by LDL-IC stimulated cells are thought to be related with the uptake of Fcγ receptor. It is known that IL-1β, TNF-α increase the vascular permeability, induce the release of IL-1 by a positive feed back mechanism by the endothelial cells; and the cell surface expression and the synthesis of procoagulant activity in the endothelial cells. Also, IL-1 may be responsible of the fibroblast and smooth muscle cell proliferation by inducing the synthesis of PDGF-AA by fibroblasts and smooth muscle cells. The pathogenic potential of this phenomenon in the progression of atherosclerosis is important. One of the important effects of cytokines is to induce the adherence of leucocytes to endothelial cells. IL-1 activates the expression of specific cell adhesion molecules (CAMs), and these vary depending on the degree of stimulus and the activation of the cell. One of these molecules is endothelial leucocyte adhesion molecule 1 (ELAM-1) which promotes the adhesion of leucocytes including monocytes to endothelial cells (18).

Recent studies suggest that immune complexes having ox-LDL are more atherogenic and the studies on this subject is still going on.

OXIDATION OF HDL

The role of HDL in oxidation is also stated. HDL can also be oxidized but less than LDL when oxidized under the same conditions and concentrations of protein (19).

Oxidation causes some structural changes in HDL as decrease in ester cholesterol, increase in oxysterol, decrease in phospholipid contents and a great increase in cholesterol:protein ratio (2). The electrophoretic mobility of ox-HDL is increased and ApoAI denaturation is also seen (20). There is evidence that HDL may have an antioxidant function, but it is found that HDL contains more lipid peroxides than LDL in the circulation. It is proposed that HDL is oxidized conserving LDL and the peroxides are transferred to liver where they are destructed (4). When oxidized, HDL shows some changes in its function. such as cytotoxicity (2), decrease in the cholesterol efflux (20) and activation of the platelets (2). It is suggested that the decrease in the stimulation of cholesterol efflux of ox-HDL is related with the denaturation of ApoAI (20). As a result the transfer of cholesterol by HDL to liver is decreased and HDL becomes more atherogenic. The protective effect of HDL in the modification and cytotoxicity of oLDL is contributed to the potential change of the lipid peroxidation products among lipoproteins (2). HDL which is negatively related with cardiovascular disease has a protective effect. When incubated with LDL it inhibits the oxidation of LDL (19) and the cytotoxic effect of already oxidized LDL.

Incubation with HDL during the oxidation the amount of lipid peroxides did not increase but the macrophage degradation which is seen with oxLDL is inhibited (2).

GLYCATION OF LIPOPROTEINS

In diabetes as a result of the increased glucose concentration non-enzymatic glycation of all proteins are enhanced. As a result another modification as non-enzymatic glycation is seen in lipoproteins (4). It is shown that human lipoproteins (HDL, LDL) show glycation when exposed to higher levels of glucose concentration and enhanced in vivo glycation has significant metabolic results. Non-enzymatic glycation of proteins contains the covalent binding of the aldehyde groups of glucose to reactive amino groups (5). The binding side is generally the lysine N-terminal (4,5). The first product is the intermediate Schiff base which is reversible. Following the Amadori rearrangement, fructose-lysine adduct is formed (5). By this binding cross linked complexes and advanced glycation end products (AGEP) and as a result hydroxy radicals are formed. These glycated LDLs are taken up by macrophages via a different receptor. In normal conditions (a) LDL particle can bind 0.5 molecule of glucose while in diabetes a LDL particle can bind 2 molecules of glucose (4). The lipid composition of diabetic and control LDL are similar. The only difference is the degree of glycation of lipoprotein and in diabetic patients it is 1:4 more than the normals (5).

Non-enzymatic glycation and oxidation are linked in vivo. The fomation of Amadori product fructose-lysine does not need oxidative conditions but the reactants related with the fructose-lysine reactions or the dissociation products need both glycation and oxidation reactions. Because browning products are produced by the reactions of glycation and oxidation following each other they are also named as "browning products" or "advanced glycation end products" (AGEP) (5). The last evidences showed that the glyco-oxidation products are formed by he reaction between the proteins and the products of free radical damage glucose (21). Some recent studies showed the induction of free radical formation by glucose and glycated proteins and the important role they play in the formation of glyco-oxidation products. Without taking the mechanism into account glyco-oxidation products are the result of glycation

and oxidative stress and are related with the cross linking of the long living proteins and enhanced chemical modification in diabetes. Recently, even the glyco-oxidative modification of the short living proteins as lipoproteins in the circulation have been shown (22).

In the formation of diabetic complications possible mechanisms of enhanced glycation and following glyco-oxidation are proposed.

One of them involves the autooxidation of glucose and fructose-lysine, the first products of Amadori rearrangement under physiological conditions and in the presence of metal ions (23). The formation of superoxide radicals and lipid peroxidation is the result of the the autooxidation of these compounds. Another possible mechanism responsible from the enhanced oxidation in diabetes is the decreased clearence of glycated LDL which prolongs the circulaton time of lipopropteins and hence makes it more susceptible to oxidation. Another mechanism for the enhanced LDL oxidation may be the trapping of LDL to intima as a result of the binding of LDL to glycated proteins by a covalent glucose derived cross binding. Also in diabetes the plasma antioxidant levels tend to be decreased (5).

Beside these in poor controlled insulin dependent and independent diabetic patients, the small dense LDL which is found more than large and bouyant LDL is more susceptible to oxidation (24).
Some investigators showed that glycated LDL is more susceptible to oxidation than non-glycated LDL and the enhanced oxidative modification maintained in the presence of high glucose levels (23). Formation of conjugated diense during the in vitro LDL oxidation is higher in diabetic patients compared to non-diabetic patients, and the concentrations of those substances are correlated with the glycation of LDL (5).

There is a good correlation between the degree of glycation and he other short- or medium-termed glycation control parameters such as the plasma glucose level, glycation of plasma proteins and HbA1c and enhanced glycation can be seen in well-controlled normolipidemic diabetic patients. When compared with the control group the ApoB glycation degree in diabetic patients was found related with the HbA1c and glycated serum protein levels. The level of incorporation of glucose to HDL and LDL apolipoproteins (ApoA-I, AII, B, C and E) is proportional with the glucose concentration and the incubation time. The glycation of LDL apoB in diabetes is twice as the non-diabetics as well (5).

The lysine residures are important for the recognition of LDL by the LDL receptor. The degress of modification of these residues are proportional to the inhibition of binding. Even 3% of these residures are modified, the binding of LDL is inhibited. The recognition of glycated LDL by the human monocyte derived macrophages, internalization and degradation is enhanced and the synthesis of ester cholesterol (CE) and accumulation in macrophages is stimulated. They are less recognized by the classical LDL receptors isolated from diabetic patients but by a different way in human macrophages causing CE accumulation and enhancing the atherosclerotic process. The synthesis of CE by macrophages is correlated by the degree of LDL glycation. The accumulation and degradation of glycated LDLs isolated from diabetic and non-diabetic individuals in fibroblasts are impaired compared to non-glycated LDL. This is related with the degree of glycation. Recognition of LDL by human fibroblasts in diabetes is impaired (5).

Diabetic patients' LDL is a more potent stimulator for the secretion of tromboxane B2 and thrombin induced platelet aggregation than the control LDL (25). Glycated LDL enhances thrombin, collagen and ADP induced platelet aggregation independent on the glucose concentration. So it is obvious that there is no linear relation of this effect with the degree of LDL glycation (5).

Glycated LDL also enhances the function of endothelial cells. Native LDL enhances the secretion of tPA of endothelial cells at a significant rate. Conversely the endothelial cells incubated with native LDL secretes PAI-1 less than the ones which are incubated with glycated LDL (5).

It is shown that glycated LDL is cleared more slowly from the circulation than the controls. The clearance rate of LDL is related with the size of LDL particule. LDL particle isolated from diabetic rabbit is smaller than the euglycemic rabbitis (26).

Enhanced glycation is observed also in VLDL and HDL and these lipoproteins are thought to effect the interaction, function and the metabolism of the cells. VLDL obtained from diabetic patients showed little changes in the VLDL lipid and apolipoprotein composition (5).

It is shown that the high affinity binding of glycated HDL to fibroblasts is diminished, and this decreases the capacity of HDL to remove cholesterol from periferic tissues (5).
Similar to the oxidized lipoproteins, a specific receptor for the glycated lipoproteins is detected in human macrophages which is different from the other scavenger receptors and called as "AGE receptors". The macrophages which express these receptors not only bind the proteins but bind all the cells which have glyco-oxidation products (5).

As stated above oxidized and glycated lipoproteins have effects on various types of cell and mechanisms. These coordinative actions show the importance of lipoproteins in the pathogenesis of atherosclerosis and diabetes. Advanced studies will be helpful in understanding the pathogenesis of atherosclerosis and diabetes better.

REFERENCES

1. Avogaro P, Bon GB, Cazzolato G. Presence of modified low density lipoprotein in humans. Arteriosclerosis 1988;8(1):79-87.
2. Morel DW. Altered LDL and HDL function induced by lipid peroxidation.In: Weber PC, ed. Vol 25. Atherosclerosis Reviews. New York: A. Leaf Raven Press, 1993:259-265.
3. Buege JA, Aust SD. Microsomal lipid peroxidation. Methods in Enzymology. 1978;52:302-310.
4. Bruckdorfer KR. Oxidized lipoproteins. In:Betteridge DJ, ed. Bailliere's Clinical Endocrinology and Metabolism Bailliere Tindall. 1995;9(4):721-737.
5. Lopes-Virella MFL, Klein RL, Virella G. Modification of lipoproteins in diabetes. Diabetes/Metabolism Reviews 1996;12(1):69-90.
6. Esterbauer H, Puhl H, Dieber-Rotheneder M, Waeg G, Rabl H. Effect of antioxidants on oxidative modification of LDL. Ann, Med, 1991;23:573-581.
7. Puhl H, Waeg G, Esterbauer H. Inhibition of LDL oxidation by vitamin E and other oxidants. In: Weber PC, ed. Atherosclerosis Reviews. Vol 25. New York: A Leaf Raven Press, 1993:277-285.
8. Morel DW, DiCorleto PE Chisolm GM. Endothelial and smooth muscle cells alter low density lipoprotein in vitro by free radical oxidation. Ateriosclerosis 1984;4:357-364.
9. Jurgerhs G, Hoff HF, Chisolm GM, Esterbauer H. Modification of human low density lipoprotein by oxidation: characterization and pathopysiologic implications. Chem Physics Lipids 1987;45:315-336.
10. Parthasarathy S, Steinbrecher UP, Barnett J, Witztum JL, Steinberg D. Essential role of phospholipase A2 activity in endothelial cell induced modification of low density lipoprotein. Proc, Natl Acad Sci (USA) 1985;82:3000-3004.
11. Esterbauer H, Gebicki J, Puhl H, Juergens G. The role of lipid peroxidation and antioxidants in oxidative modification of LDL. Free Rad Biol Med 1992;13:341-390.
12. Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL. Beyond cholesterol: modifications of low-density lipoprotein that increase its atherogenicity. N Engl J Med 1989;320:915-924.
13. Kugiyama K, Sakamoto T, Musumi I, et al. Transferable lipids in oxidized LDL stimulate PAI-1 and inhibit tPA release from endothelial cells. Circ Res 1993;73:335-343.
14. Levin EG, Miles LA, Fless GM, et al. Lipoproteins inhibits the secretion of tissue plasminogen activator from human endothelial cells. Arterioscler Thromb 1994;14:438-442.
15. Steinbrecher UP, Lougheed M, Zhang H. Biochemical basis of the receptor interaction and altered intracellular catabolism of oxidized LDL. In: Weber PC, ed. Vol 25. New York: A Leaf Raven Press, 1993;247-257.
16. Salonen JT, Yla-Herttualas Yamamoto R, et al. Autoantibody against oxidized LDL and progression of carotid atherosclerosis. Lancet 1992;339:883-887.
17. Lopes-Virella MF, Griffith RL, Shunk KA, Virella GT. Enhanced uptake and impaired intracellular metabolism of low density lipoprotein complexed with anti-low densitiy lipoprotein antibodies. Arterioscler Thromb 1991;11:1356-1367.
18. Bevilacqua MP, Stengelin S, Gimbrone MA. Jr, Seed B. Endothelial leucocyte adhesion molecule 1: and inducible receptor for neutrophils related to complement regulatory proteins and lectins. Science 1989;243:1160-1165.
19. Parthasarathy S, Barnett J, Fong LH. High density lipoprotein inhibits the oxidative modification of low density lipoprotein. Biochim Biophys Acta 1990;1044:275-283.
20. Nagano Y, Arai H, Kita T. High density lipoprotein loses its effect to stimulate efflux of cholesterol from foam cells after oxidative modification.Proc Natl Acad Sci (USA.) 1991;88:6457-6461.
21. Fu M-X, Knecht KJ, Lyons TJ, Torphe SR, Baynes JW. Role of oxygen in the cross-linking and chemical modification of collagen by glucose. Diabetes 1994;43:676-683.
22. Bucala R, Makita Z, Koschinsky T, Cerami A, Valassara H. Lipid advanced glycation: pathway for lipid oxidation in vivo. Proc Natl Acad Sci (USA) 1993;90:6434-6438.
23. Hunt JV, Smith CCT, Wolff SP. Autooxidative glycation and possible involvement of peroxidases and free radicals in LDL modification by glucose. Diabetes 1990;39:1420-1424.
24. de Graaf J, Hak-Lemmers HLM, Hectors MPC, Demacker PNM, Hendriks JCM, Stalenhoef AFH. Enhanced susceptibility to in vitro oxidation of the dense low density lipoprotein subfraction in healthy subjects. Arterioscler Thromb 1991;11:298-306.
25. Watanabe J, Wohltmann HJ, Klein RL, Colwell JA, Lopes- Virella MF. Enhancement of platelet aggregation by low density lipoproteins from IDDM patients. Diabetes 1988;37:1652-1657.
26. Kortland W, Benschop C, van Rijn HJM, Erkelens DW. Glycated LDL catabolism is increased in rabbits with alloxan-induced diabetes mellitus. Diabetologia 1992;35:202-207.