

AUTOANTIBODIES AGAINST OXIDIZED LDL (oLAB)

1. Characteristics of oLAB

Antibodies to low density lipoproteins (oLAB) are detectable in practically every human being of all ages. It has been speculated that these antibodies are involved in a protective process taking place when low density lipoprotein is oxidized to oLDL.

oLDL is generated by the action of free radicals and results in the appearance of modified epitopes which are immunogenic. In consequence, oxidized LDL antibodies (oLAB) are generated.

Antibodies to oLDL have been described in various disorders. Although their clinical significance has been demonstrated only in carotid and coronary atherosclerosis (2, 25, 36, 44), it has been proposed that they represent a biological marker of lipid peroxidation.

Atherosclerosis is initiated by the oxidation of LDL. The oLDL is accumulated in macrophages, which turn into foam cells afterwards. Foam cells are the initial step in the formation of atherosclerotic plaques.

It is estimated, that this mechanism stimulates the immune system. oLDL-specific IgG could be isolated from human atherosclerotic lesions. On the other hand, human plaques showed positive reactions against oLDL-specific antibodies (47).

Elevated oLAB-concentrations could also be estimated in sera of patients with coronary diseases (47), hypertension (35), peripheral artery blockage (32), carotis-atherosclerosis (44), diabetes (28, 33), systemic lupus erythematosus (41), preeclampsia (37) and hyperthyroid patients. Alpha-tocopherol (vitamin E) has a clear protective effect on lipid peroxidation and is supported by the increase of oLAB titers (9, 46).

Reduced oLAB-concentrations were reported in the acute phase of a myocardial infarction (16), ischemic stroke (5) and acute septicemia (12). Radicals are produced by these stress situations, which cause lipid peroxidation. These oxidation products react with oLAB and decrease their concentrations.

2. Biosynthesis of oLAB

Free radicals are produced by the organism as a result of oxidative stress. The unpaired electrons of such radicals cause a very high reactivity against proteins, DNA, polyunsaturated fatty acids (PUFA) and lipids.

The low density lipoproteins (LDL) are very sensitive on these radical mediated lipid peroxidations, whereby oxidized LDL (oLDL) is produced as a result.

The immunogenicity of oLDL is very high, therefore oLDL-specific antibodies (oLAB) are produced by the immune system.

These oLABs are measurable in the circulation and reflect in vivo-oxidation processes.

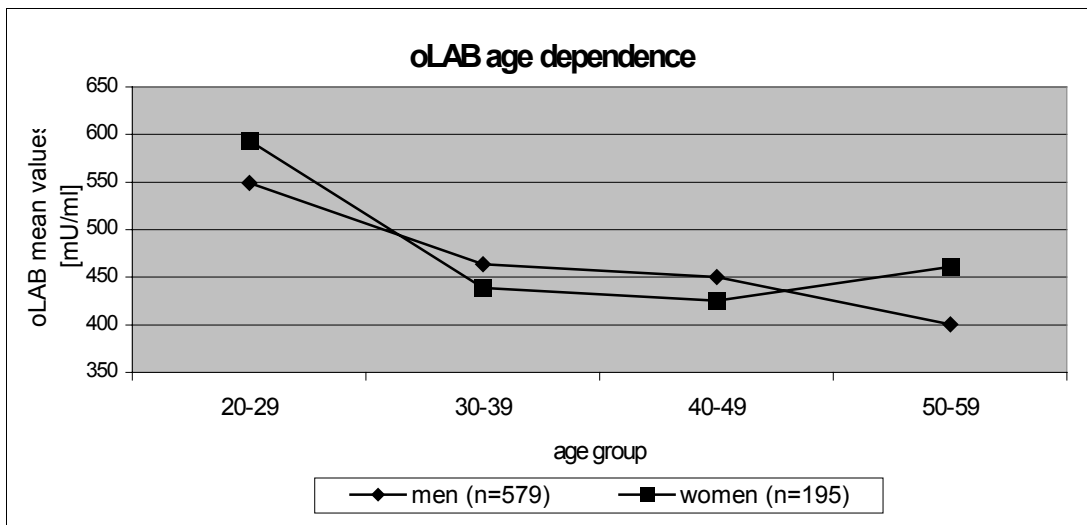
3. Function and relevance of oLAB

The involvement of lipid peroxidation (LPO) into the pathogenesis of atherosclerosis is generally accepted (42, 45).

Several publications describe pathological involvement of such antibodies into cardiovascular diseases (5, 12, 16, 28, 32, 33, 35, 37, 41, 44, 47). Salonen et al (44) found high levels of oLAB predictive for the progression of atherosclerosis. About half of the people enjoying western lifestyle are currently dying of myocardial infarcts or ischemic strokes caused by artery obstruction derived from atherosclerotic plaques (25, 47). As oLABs are obviously an immunogenic fingerprint of LPO and contribute at least to the progression of atherosclerosis, epidemiologic investigations have been performed to clarify the incidence and distribution of oLAB in healthy subjects.

During a preventive medicine screening in Vienna (Austria) 1995, the normal distribution of oLAB of 800 healthy man and women with an age from 20 to 60 years has been determined (14, 19).

Results are shown in the following graph:



oLAB concentrations were inverse proportional to the ages of the people.

In the age group 20-40 years, oLAB values decreased significantly, which could indicate first steps of atherosclerosis. High oLAB concentrations in young people could be interpreted as a protection mechanism of the organism.

Normal values for oLAB in this investigation showed to be in the wide range of 20 - 800 mU/ml. The individual oLAB titer is dependent on different factors, e.g. age, oxidative status (antioxidant level), vitamine supplies, nutrition habits, smoking (very low oLAB titers in smokers), exercises, and individual immunoresponses.

Due to these factors, every individual seems to have its own oLAB level.

Furthermore it remains unknown, if autoantibodies are removed from the circulation by tissue-adsorption, and if the measurement results reflect the total oLAB amount thereby.

It is well known, that ageing is at least partly a free radical mediated process (11, 14, 19, 47). The involvement of lipid peroxidation into that process is therefore conclusive. This

hypothesis is further supported by the fact, that chain breaking antioxidants, such as tocopherol, can inhibit lipid peroxidation (9, 46).

oLAB is also an interesting parameter for monitoring, e.g. before transplantation, and follow up. In one study, autoantibody serum levels decreased at three months after transplantation in all patients (6).

Patients that develop a chronic vascular rejection, oLAB increased constantly, and at 24 months after transplantation exceeded pretransplant values by 52% (6).

4. Clinical Applications and Pathophysiology

Autoantibodies to oxidized LDL are generated and influenced by several diseases:

- ⇒ atherosclerosis
A correlation of oLAB titers and progression of atherosclerosis was found, measured sonographically as the increase of intimal media thickness.
oLAB may serve as a useful tool in predicting cardiological risks like infarction or stenosis.
- ⇒ myocardial infarction
A transient decrease of oLAB was found during myocardial infarction after lysis, which was inversely correlated with the CK-MB mass index.
- ⇒ coronary diseases (e.g. chronic periaortitis)
- ⇒ ischemic stroke
- ⇒ peripheral artery blockage
- ⇒ essential hypertension
- ⇒ acute septicemia
- ⇒ diabetes
- ⇒ acute and chronic renal failure
- ⇒ systemic lupus erythematosus
- ⇒ hyperthyroidism
- ⇒ rejection of organs after transplantation (kidney, liver, heart)
- ⇒ preeclampsia

The diagnostic value of determining oLAB lies in the clarification of the complex autoxidative processes during or after these diseases.

Sometimes the publicised research results contradict each other. However, these results were based upon different assay methods, which made direct comparisons difficult.

The assays differed in oxidation mechanisms, incubation temperatures, blockages, sample dilutions and calculation modes (34).

A review of clinical applications for oLAB is publicised in (38).

6. General informations on LDL oxidation

An important function of LDL and oLDL lays in its enhanced uptake by macrophages. oLDL is recognised by the scavenger receptors and internalized by the macrophages which then become lipid loaden foam cells. Macrophages themselves are also responsible for the oxidation of LDL.

oLDL has chemotactic properties for monocytes and is cytotoxic to endothelial and smooth muscle cells.

Parallel to foam cell formation, autoantibodies to oxidized LDL become present in the human serum.

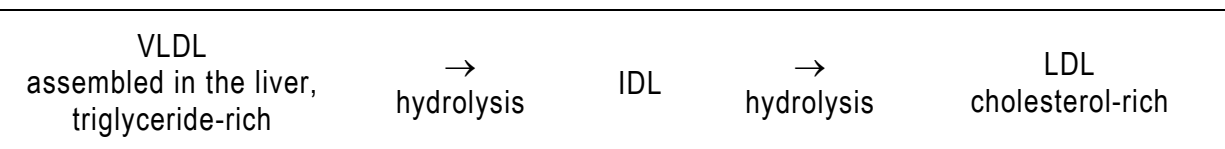
6.1. LDL biosynthesis

The liver assembles triglyceride-rich, very low density lipoproteins (VLDL) and secretes them into the circulation.

The main biological function of VLDL is to supply the peripheral tissues with fatty acids. Enzymes (lipoprotein lipases) on the surface of the vascular endothelial cells hydrolyse the VLDL triglycerides to fatty acids.

With increasing hydrolysis, the VLDL lose most of their triglycerids and progressively change into lipoproteins with intermediate density (IDL) and finally to cholesterol-rich LDL.

VLDL and IDL have a short half life - removed from circulation they disappear within hours. LDL circulate in the blood for 2 days before they are cleared.



Serum LDL concentrations are normally around 3 mg/ml. LDL carries about 60% of the total serum cholesterol.

Uptake of LDL by cells occur via receptor-mediated pathways and by nonspecific endocytosis. LDL receptors are present on most cells and the highest concentration is found in the liver - $\frac{3}{4}$ of the total LDL amount is removed from the bloodstream by the liver.

The liver converts most of the LDL cholesterol to bile acids, which are then secreted into the duodenum.

The cholesterol of LDL is used by all cells as an essential part of their cell membranes and in specialised cells for biosynthesis of steroid hormones.

Imbalance in cholesterol homeostasis results from defects in the LDL receptor gene and leads to to hypercholesterolemia. This defficiency of the receptor reduces the clearance rate of LDL.

6.2. Composition of LDL molecules

LDL molecules are spherical particles with 19 - 25 nm diameter and with a molecular weight of 1.8 - 2.8 million Dalton.

Native LDL consist of:

- phospholipids.
- triglycerids.
- cholesterol - as free cholesterol and cholesterol ester.
- free fatty acids - as 50% polyunsaturated fatty acids (PUFA), mainly linoic acid.
The fatty acid content of LDL varies considerably with dietary habits.
- proteins - e.g. Apolipoprotein B (Apo B).
- lipophilic antioxidants - they protect the PUFAs in LDL against free radical attack and oxidation.

Each LDL particle contains cholesterylesters and triglycerides, which form a central lipophilic core. This core is surrounded by a monolayer of phospholipid molecules and cholesterol. The polar heads of the phospholipid molecules are located at the surface of the LDL particle and contribute to its ability to emulsify.

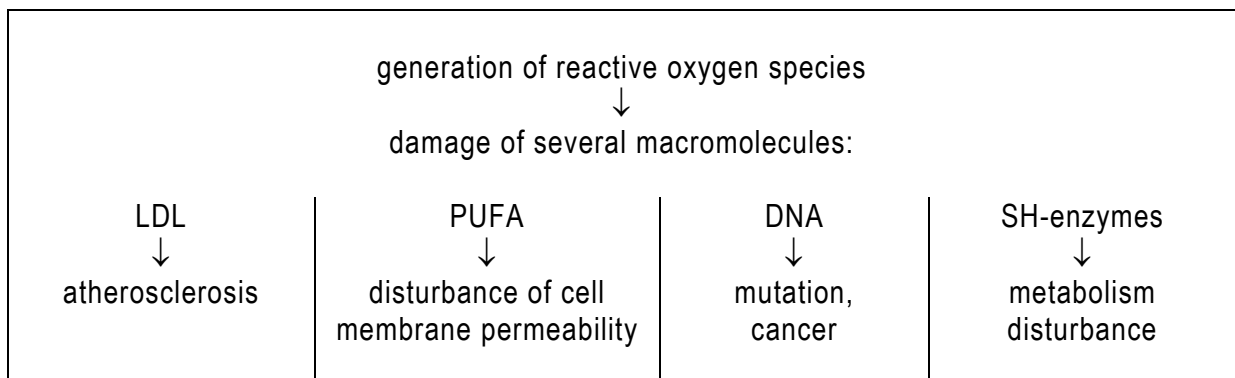
Apo B is embedded in the outer layer of LDL. This molecule could be seen as an octopus embracing the whole surface of LDL. Apo B is a large protein of 4536 amino acids and is glycosylated.

6.3. Chemistry of lipid peroxidation

Oxidative processes result in the generation of different reactive oxygen species:

- O_2^{2-} superoxid-anion
- $HO\cdot$ hydroxyl-radical
- 1O_2 singulet-oxygen
- H_2O_2 hydrogenperoxide

These high-reactive molecules cause several damages to cell organelles:



The oxidation of LDL leads to changes in rheology, permeability and stimulation of the cell membranes, thus the interaction between the cells and the extracellular media is affected.

The chemistry of lipid peroxidation is a very complex process and a number of chain reactions contribute to its major events (Fig. 1):

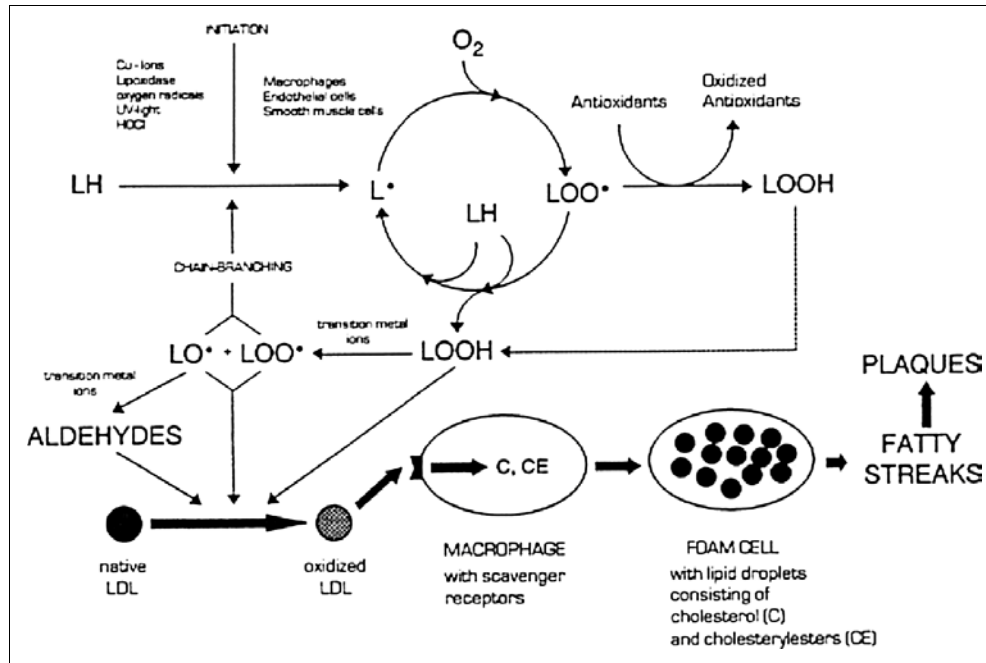


Fig. 1: Summary of the main events of lipid peroxidation and foam cell formation. The oLDL particle is not only rapidly uptaken by macrophages via the scavenger receptor, but has also antigenic properties.

The main steps of lipid peroxidation are:

1. Reactive oxygen species (O_2 , H_2O_2) trigger chain reactions in polyunsaturated fatty acids (PUFAs) which lead to the formation of organic peroxides and highly reactive aldehyds.
2. This free radical action depletes lipids from their antioxidants (Vitamin E, carotinoids).
3. End product of this chain reactions are the following aldehyds:
 - 25 % hexanal
 - 12.5 % 4-hydroxynonenal (4-HNE)
 - 42 % malondialdehyde (MDA).
 MDA can bind covalently to amino acid residues of Apo B and forms immunogenic epitopes - oLDL turns to be antigenic.

Lipid peroxidation presumably starts with the PUFAs in LDL surface phospholipids, and then propagates to the core lipids, resulting in oxidative modification not only of the PUFAs, but also of the cholesterol moiety itself and of phospholipids, and modification and degradation of Apo B.

6.4. Mechanism of LDL Oxidation

In vitro: Endothelial cells, smooth muscle cells and especially macrophages are all capable of oxidizing LDL in vitro. In vitro, LDL can bind copper or iron, which promote rapid lipid peroxidation. It is not known whether sufficient free copper or iron exist in vivo to promote LDL oxidation. Several mechanisms are probably involved. For example, release of superoxide anion from endothelial cells might be responsible for initiation of oxidation in some settings, and thiols in others.

Fig. 2 gives an overview of the mechanisms involved, which lead to oxidative modification of LDL and foam cell formation:

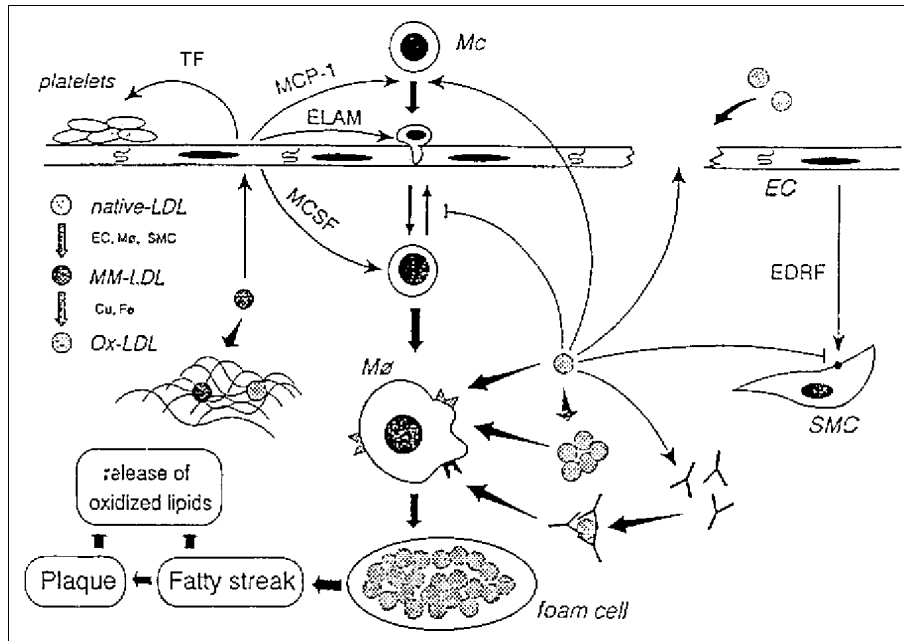


Fig. 2: Mechanisms leading to oxidative modification of LDL and foam cell formation.

In vivo: Oxidative modification of LDL occurs primarily in the arterial intima, and in microdomains sequestered from antioxidants in plasma. Because of the antioxidants present, LDL is probably little oxidized in plasma.

In vivo, whether or not LDL becomes oxidized is a question of balance between the extent of pro-oxidant challenge and the capacity of antioxidant defenses. The balance of these forces determines the extent of arterial wall modification of LDL. It is not clearly known where LDL is oxidized or what mechanisms lead to LDL oxidation in vivo.

Occlusions and plaques which form in the intima regions of the major arteries are made up of cells altered in their appearance by internalized lipids - they are known as foam cells. These foam cells were identified as macrophages derived from monocytes circulating in the blood.

Formation of foam cells:

1. Monocytes invade from the bloodstream into subendothelial space and become resistant macrophages.
2. They take up lipids and lipoproteins infiltrated and deposited in those regions.
3. Uptake leads to intracellular cholesteryl ester accumulation.

6.5. In vitro oxidation of LDL

There are several ways of achieving oLDL in vitro - either by modifying LDL with MDA, or by oxidising LDL with Cu^{2+} ions.

Here are the phases during copper oxidation:

1. Lag phase:
The PUFAs are protected against oxidation by endogenous antioxidants.
Antioxidants: Tocopherol (vitamin E), carotenoids, ubiquinol, ascorbate.
2. Propagation phase:
When the antioxidants are exhausted, LDLs become unprotected. PUFAs are oxidized.

3. Decomposition phase:

When most of the PUFAs are oxidized (70 - 80%) the aldehyd content increases.

7. Implications

oLAB

BIOMEDICA oLAB PUBLICATIONS

Autoantibodies to oxidized low density lipoproteins in IDDM are inversely related to metabolic control and microvascular complications

(1) *Festa et al., Diabetologia (1998) 41:350-356*

oLDL specific immune complexes were found exclusively in antibody-negative as compared to antibody-positive patients. The data demonstrate an inverse relationship between free oLDL antibodies and the severity of the disease.

Autoantibodies against oxidized low density lipoproteins in older stroke patients

(2) *Cherubini et al., J. Am. Geriatr. Soc. (1997) 45:125*

oLAB have been studied in various disorders, such as carotid atherosclerosis, hyperlipidemia, and essential hypertension. oLAB titers in stroke patients were significantly lower than in control subjects.

Quantitative determination of oLAB titers in various animal species

(3) *Tatzber et al., BioFactors (1997) 6:125-130*

The protein A modification of oLAB allows direct reading of animal oLAB titers from human calibrators. Preliminary results obtained show that immunisation experiments with oLDL give serum titers in animals, which are in the same order of magnitude as human sera with high oLAB concentrations.

Inverse correlation of malondialdehyde (MDA) and anti-Cu²⁺ oxidised low-density lipoprotein (LDL) immunoglobulin G (IgG) antibodies in transplantation patients

(4) *Khoschorur et al., Med. Sci. Res. (1996) 24:851-854*

Positive correlations were found in patients with transplanted livers between MDA and neopterin, and inverse correlations between oLAB and MDA.

Autoantibodies against oxidized low-density lipoproteins in acute stroke patients

(5) *Cherubini et al., poster presented at the Lipoprotein Oxidation and Atherosclerosis Meeting 1996 in Pavia*

Our results indicate that oLAB titers in stroke patients were significantly lower than in control subjects.

Serum levels of antibodies against oxidized LDL in kidney graft recipients

(6) *Zeina et al., poster presented at the Lipoprotein Oxidation and Atherosclerosis Meeting 1996 in Pavia*

The aim of this study was to investigate the production of oLAB in kidney graft recipients before and after transplantation, and their possible relation to the outcome of transplantation.

Cu²⁺ mediated LDL Oxidation generates epitopes, which are recognized by human IgG molecules in vitro

(7) *Mißbichler et al., poster presented at the Oxidative Stress Workshop 1996 in Seggau*

The scope of this study was to investigate reactions of different human sera with LDL of various oxidation stages. The same or at least very similar epitopes as those occurring in vivo are generated during Cu²⁺ mediated lipid peroxidation.

Inverse Correlation of MDA and anti Cu²⁺ oxidized LDL IgG antibodies in transplantation patients

(8) *Khoschsorur et al., poster presented at the Oxidative Stress Workshop 1996 in Seggau*

Four patients with liver and heart allograft transplantation were included in the study. In the patients with fatal outcome, we found strongly increasing levels of neopterin and MDA, while elastase and oLAB showed decreasing values.

Effect of supplementation with β-carotene and α-tocopherol in Iranian subjects

(9) *Shokoufeh et al., poster presented at the Oxidative Stress Workshop 1996 in Seggau*

While β-carotene had the limited protective effect on the lipid peroxidation, α-tocopherol had a clear prohibitive effect supported by the increase of lag phase as well as oLAB and the decrease of MDA.

Epitopes of oxidized Lipoproteins in vivo are partly represented by MDA-LDL and oxidized LDL

(10) *Resch et al., poster presented at the Oxidative Stress Workshop 1996 in Seggau*

Neither MDA-LDL nor oLDL is fully representative for all antigenic structures formed in vivo, and it is questionable, if both together are.

Antibodies against oxidized low density lipoprotein (oLAB) are quantitatively removable from human sera by oxidized and aged erythrocyte membranes.

(11) *Schmidl et al., poster presented at the Oxidative Stress Workshop 1996 in Seggau*

Modified erythrocytes can act as primary antigens for oLAB in vivo. The biological function of these antibodies may be to remove damaged or modified cell membranes from circulation and/or tissue.

Septicemic patients show a decrease in neopterin levels and an increase in autoantibodies to oxidized LDL (oLAB) after successful therapeutic intervention

(12) *Strohmaier et al., poster presented at the Oxidative Stress Workshop 1996 in Seggau*

Circulating oLAB were significantly lower in acute septicemia compared with the timepoint of release from the intensive care unit. If the patients faced a fatal outcome of septicemia, oLAB remained constantly low or showed a further decrease in titres.

Post-traumatic dynamic change of the titer of autoantibodies against oxidized low density lipoproteins; unspecific or organ specific consequence of injury?

(13) *Wildburger et al., poster presented at the Oxidative Stress Workshop 1996 in Seggau*

While the initial post-traumatic decrease of oLAB was uncertain in patients with traumatic brain injury (TBI) alone, it was obvious in those with bone fractures or combined injury.

Age dependent decrease of antibodies to oxidized LDL (oLAB) in healthy people

(14) *Temmel et al., poster presented at the Oxidative Stress Workshop 1996 in Seggau*

In clinically healthy people we found an inverse age correlation of oLAB in both sexes, which was less pronounced than the direct proportionality of cholesterol and age.

Antibodies to oxidized LDL (oLAB) in animals

(15) *Tatzber et al., poster presented at the Oxidative Stress Workshop 1996 in Seggau*

In general, no differences were observed concerning specificity and avidity of oLAB in animals compared with humans.

Transient reduction of autoantibodies against oxidized LDL in patients with acute myocardial infarction

(16) *Schumacher et al., Free Radical Biology & Medicine (1995) 18 (6): 1087-1091*

The decrease of oLAB appears to be a marker for the severity of myocardial infarction.

Autoantibodies to oxidized low density lipoprotein

(17) *Tatzber et al., Free Radicals, Lipoprotein Oxidation and Atherosclerosis (1995) 9: 245-262*

It can be concluded that oLAB play an important role in atherosclerosis progression and that they probably influence other disorders, such as essential hypertension and chronic periaortitis.

Determinazione immunoenzimatica di autoanticorpi anti LDL ossidate (oLAB), nel siero

(18) *Crapanzano et al., poster presented at the XLV Congresso Nazionale AIPaC 1995*

In this study an oLAB ELISA was validated with patients having different diseases.

Antibodies against oxidized LDL (oLAB) in Viennese working people

(19) *Tatzber et al., poster presented at the Austrian Society for Allergy and Immunology (1995)*

As young people have statistically significant higher titers than elderly ones, a protective function of oLAB is assumable. The decrease of titers in people of 20 to 40 years of age may be associated with the onset of atherosclerotic processes as described by other authors.

Determination of autoantibodies against oxidized LDL in sera samples of injured patients by immunoassay

(20) *Borovic et al., poster presented at the Austrian Society for Allergy and Immunology (1995)*

oLAB were determined in pooled samples of normal human sera, human seras obtained from patients with bone fracture, head injury and combined head and bone injury.

Human Autoantibodies against oxidized LDL: Implications of sex and life habits

(21) *Tatzber et al., poster presented at the Austrian Society for Allergy and Immunology (1993)*

We found a significant increase of oLAB titers in men during rehabilitation, which could not be found in females.

Presence of foam cells containing oxidized low density lipoprotein in the synovial membrane from patients with rheumatoid arthritis

(22) *Winyard et al., Annals of the Rheumatic Diseases (1993) 52:677-680*

The findings in all rheumatoid patients studied suggest that atherosclerosis and rheumatoid arthritis have analogous pathogenetic features.

oLAB

GENERAL oLDL AND oLAB PUBLICATIONS

Increased lipid peroxidation and impaired antioxidant enzyme function is associated with pathological liver injury in experimental alcoholic liver disease in rats fed diets high in corn oil and fish oil

(23) *Polavarpu et al., Hepatology (1998) 27:1317-1323*

The decrease in activity of antioxidant enzymes observed in animals fed diets high in polyunsaturated fatty acids and ethanol could possibly increase the susceptibility to oxidative damage and further contribute to ethanol-induced liver injury.

Failure of antioxidant therapy to attenuate interstitial disease in rats with reversible nephrotic syndrome

(24) *Drukker et al., J. Am. Soc. Nephrol. (1998) 9: 243-251*

In two studies (single-dose and multidose) it was determined, whether oLDL contributes to the tubulointerstitial changes seen in rats during the acute phase of acute puromycin aminonucleoside nephrosis.

In search of biological markers of high-risk carotid artery atherosclerotic plaque: enhanced LDL oxidation

(25) *Chiesa et al., Ann. Vasc. Surg. (1998) 12:1-9.*

Biochemical markers of in vivo LDL oxidation are linked to some clinical features of carotid artery atherosclerotic plaques, such as the degree of vessel stenosis and the presence and severity of ulceration.

Lipoperoxidation as a measure of free radical injury in otitis media

(26) *Haddad, The Laryngoscope (1998) 108:524-530*

Lipoperoxidation may contribute to middle ear inflammation for a significant period of time after acute infection.

Lysophosphatidylcholine is involved in the antigenicity of oxidized LDL

(27) *Wu et al., Arterioscler. Thromb. Vasc. Biol. (1998) 18:626-630*

The presence of antibodies against lysophosphatidylcholine (LPC) is demonstrated, both of the IgG and IgM isotype, in 210 healthy individuals. LPC competitively inhibited anti-oLDL reactivity, which indicates that LPC may explain a significant part of the immune-stimulatory properties of oLDL.

Immune response to glycated and oxidized LDL in IDDM patients with and without renal disease

(28) *Korpinen et al., Diabetes Care (1997) 20:1168-1171*

Antibodies to glycated and oxidized LDL do not seem to associate with diabetic nephropathy or nephropathy-related macroangiopathy.

Relationships among oxidation of low-density lipoprotein, antioxidant protection, and atherosclerosis

(29) *Esterbauer et al., Advances in Pharmacology (1997)38:425-456*

A description of the LDL oxidation hypothesis, the possible influence of oLDL and antioxidants on atherogenesis, and the assessment and relevance of in vitro-measured LDL oxidation indices is given. Epidemiological studies on relationships of antioxidant consumption and blood antioxidant concentration with cardiovascular disease are summarized.

Reduced progression of atherosclerosis in apolipoprotein E-deficient mice following consumption of red wine, or its polyphenols quercetin or catechin, is associated with reduced susceptibility of LDL to oxidation and aggregation.

(30) *Hayek et al., Arterioscler. Thromb. Vasc. Biol. (1997) 17:2744-2752*

Dietary consumption by apolipoprotein E deficient mice of red wine or its polyphenolic flavonoids quercetin and, to a lesser extent, catechin leads to attenuation in the development of the atherosclerotic lesion, and this effect is associated with reduced susceptibility of their LDL to oxidation and aggregation.

Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival - 4

(31) *Singh et al., Cardiovasc. Drugs Ther. (1997) 11:485-491*

Fish oil and mustard oil, possibly due to the presence of n-3 fatty acids, may provide rapid protective effects in patients with AMI.

Patients with early-onset peripheral vascular disease have increased levels of autoantibodies against oxidized LDL

(32) *Bergmark et al., Arterioscl. Thromb. Vasc. Biol. (1995) 15: 441-445*

Autoantibody levels against oLDL are related against other risk factors for peripheral arterial occlusive diseases, such as hereditary factors, lipoprotein levels, and smoking.

Autoantibodies against oxidatively modified low density lipoproteins in non insulin dependent diabetes mellitus (NIDDM)

(33) *Bellomo et al., Diabetes (1995) 44: 60-66*

In NIDDM patients an enhanced LDL oxidation occurs in vivo and LDL glycation may represent a predisposing event that facilitates subsequent oxidative modifications.

Autoantibodies against oxidized low density lipoprotein: a review of clinical findings and assay methodology

(34) *Craig, Journal of Clinical Laboratory Analysis (1995) 9:70-74*

The measurement of oLDL promises to yield important information concerning the understanding of the development and/or consequences of atherosclerosis. At present, assays are not standardized, therefore comparison and interpretation of data between studies is difficult at best.

Presence of autoantibodies against oxidatively-modified LDL in essential hypertension: a biochemical signature of an enhanced in vivo LDL oxidation

(35) *Maggi et al., J. Hypertension (1994) 11: 1103*

During the early phases of hypertension development, LDL undergo oxidation in vivo that is mirrored by the generation of autoantibodies against epitopes of oxidized LDL. The oxidation process appears specific for LDL and may be relevant for both the progression of hypertension and for the development of atherosclerosis that often complicates hypertension itself.

LDL oxidation in patients with severe carotid atherosclerosis – a study of in vitro and in vivo oxidation markers

(36) *Maggi et al., Arterioscler. Thromb. (1994) 14:1-8*

Patients develop oLAB and, despite an apparently „normal“ oxidation profile in vitro, support the occurrence of an enhanced LDL oxidation in vivo.

Preeclampsia and serum antibodies to oxidized low-density lipoprotein

(37) *Branch et al., The Lancet (1994) 343: 645-646*

Significantly higher mean titers of autoantibodies to MDA-LDL were detected in the sera of preeclamptic patients, than in healthy pregnant women.

Autoantibodies against oxidatively-modified LDL in uremic patients undergoing dialysis

(38) *Maggi et al., Kidney Int. (1994) 46: 869-876*

CRF patients on dialytic treatment, and particularly on hemodialysis, develop autoantibodies against oxidatively-modified LDL and support the occurrence of an enhanced LDL oxidation in vivo.

The oxidation hypothesis of atherosclerosis

(39) *Witztum, The Lancet (1994) 344: 793-795*

The testing of the oxidation hypothesis is at an early phase. It is not yet possible to make specific recommendations to the general public.

Lipoprotein, Oxidation and Atherosclerosis

(40) *Finardi et al., Pavia conference (1994)*

Summary of 26 lectures and 36 posters.

Crossreaction between antibodies to oxidized low-density lipoprotein and to cardiolipin in systemic lupus erythematosus (SLE)

(41) *Vaarala et al., The Lancet (1993) 341: 923-925*

A crossreactivity is suggested between antiphospholipid antibodies, which are closely associated with thrombosis in SLE, and antibodies to oLDL, thus providing a possible link between thrombotic and atherosclerotic complications in SLE.

The pathogenesis of atherosclerosis: a perspective for the 1990s

(42) *Ross, Nature (1993) 362:801-809*

This review states of what is known of the cells and molecules involved in atherosclerosis and what can be done to prevent and treat this disease.

Specificity of autoantibodies against oxidized LDL as an additional marker for atherosclerotic risk

(43) *Maggi et al., Coronary Artery Disease (1993) 4:1119-1122*

The occurrence of oLAB could be specifically related to the promotion and progression of atherosclerosis and is not a simple epiphenomenon of any oxidative process occurring in vivo.

Autoantibody against oxidized LDL and progression of carotid atherosclerosis

(44) *Salonen et al., The Lancet (1992) 339: 883-887*

The titer of autoantibodies to MDA-LDL was an independent predictor of the progression of carotid atherosclerosis in Finnish men. The data provide further support for a role of oxidatively modified LDL in atherogenesis.

Lipid peroxidation and its role in atherosclerosis

(45) *Esterbauer, Nutr. Metab. Cardiovasc. Dis. (1992) 2:55-57*

oLDL is a risk factor of atherosclerosis and consequently prevention of oxidation by antioxidants could have therapeutic potential.

Inhibition of LDL oxidation by antioxidants

(46) Esterbauer et al., In: "Free Radicals and aging" (Ed: I. Emerit & B. Chance) (1992) pp 145-157, Birkhäuser Verlag, Basel(1992)

Antioxidants like α -tocopherol are able to protect LDL against oxidation. Yet the efficiency of α -tocopherol to protect LDL shows strong individual variation.

Antibodies to oxidized low-density lipoprotein and ceroid in chronic periaortitis

(47) Parums et al., *Arch. Pathol. Lab. Med.* (1990) 144: 383-387

Chronic periaortitis is accompanied by autoallergy to ceroid, which is probably at least partly composed of low-density lipoprotein oxidized within the human atherosclerotic plaque. A number of middle-aged and elderly people without chronic periaortitis also have such antibodies.

Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity

(48) Steinberg et al., *N. Engl. J. Med.* (1989) 320:915-924

Research developments are summarized, and the promising clues that may lead to therapeutic measures in the near future that would add to or be synergistic with measures to lower plasma cholesterol levels.