Oxidized LDL and cardiovascular risk

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Outlook

- Introduction
- Oxidized LDL: definition, types, dynamics, receptors
- Proatherogenic mechanisms
- Assessment
- Clinical and experimental studies
- Reducing ox-LDL
- Conclusions
Introduction

- **Atherosclerosis** - the most important cause of cardiovascular morbidity and mortality.
- Occurs due to accumulation of lipids deposits (mainly cholesterol) in macrophages from large and medium sized arteries.
- Definition: a material rich in fibrin and lipids is deposited on the arterial wall → abnormal thickening and stiffening of the arterial walls.
- Consequences: coronary heart disease, stroke, peripheral arterial disease.
Mortality in males

- Coronary heart disease: 20%
- Stroke: 10%
- Other CVD: 12%
- Stomach cancer: 2%
- Colo-rectal cancer: 2%
- Other cancer: 13%
- Respiratory disease: 7%
- Injuries and poisoning: 10%
- All other causes: 20%
Mortality in women

ESC, 2012
Stages of atherosclerotic plaque formation

- Endothelial dysfunction
- Fatty streak
- Fibrous plaque
- Plaque rupture
Endothelial dysfunction

- LDL enter the vascular intima
- LDL oxidation and glycation
- Triggering an inflammatory response
- FOAM CELL formation

FATTY STREAK

- smooth muscle cell migration into the intima
- extracellular matrix synthesis

Fibrous plaque: fatty streak, connective tissue, smooth muscle cells

complications

rupture

hemorrhage

aneurism

-thrombosis
-embolization

infarction

Mozos, 2015
Oxidized LDL: definition

Particle derived from circulating LDL, containing peroxides or their degradation products (Parthasarati et al, 2010)

Marker of oxidative stress

The CAUSE of atherosclerosis (Steinberg et al, 1989; Steinberg, 2009)

Atherogenic form of LDL
The dynamics of oxidized LDL during atherogenesis
The dynamics of oxidized LDL

mmLDL $\rightarrow$ molLDL $\rightarrow$ oXLDL

TLR4

LOX-1, SR-A1,2 CD36

Zmysłowski et al, 2017
Stages of LDL oxidation

1. **Lag phase**: endogenous antioxidants are consumed (vitamin E)

2. **Proliferation phase**: PUFAs can be oxidized to fatty acid fragments, oxidized phospholipids and oxygen free radicals

3. **Decomposition stage**: FA fragments converted to aldehyde, which interacts with LYS (apoB) to form new epitopes

Gao et al, 2017
Initiating Events in the Development of a Fatty Streak Lesion
MM-LDL (OxLDL) may be transferred between vessel wall and plasma

(a) Early stages

Partial degradation of OxLDL by macrophages

(b) Advanced lesion

Transient release of OxLDL

(c) Plaque rapture
Types of oxidized LDL

Parthasarati et al, 2010
List of lipid/protein oxidation products generated during the oxidation of LDL

**Fatty acid oxidation products**: free and esterified fatty acid peroxides, free and esterified fatty acid hydroxides, prostaglandin-like products (isoprostanes in free and esterified forms), aldehydes (MDA)

**Lipid derived products**: lysophosphatidylcholine, cholesterol oxidation products (7 keto cholesterol), internally modified phosphatidyl ethanolamine/serine products

**Protein oxidation products**: protein carbonyls, non-enzymatic proteolyzed fragments, modified cysteine, cystine, histidine, methionine, lysine, arginine, tryptophan, and tyrosine, protein cross-links due to tyrosine cross-links as well as due to bifunctional aldehydes, ceroids (lipofuscins)

**Other changes**: increased buoyant density, increased negative charge, loss of characteristic yellow color (human), loss of enzyme activities associated with LDL

Parthasarati et al, 2010
O parte din LDL pătruns la nivel vascular este oxidată, rezultând LDL oxidat, captat de macrofage care se transformă în celule SPUMOASE (Morel et al, 1983; Steinberg et al, 1997).


Apare datorită formării de specii reactive de oxigen și azot de către celulele endoteliale (Karimi et al, 2013).

Vitamina E reduce oxidarea LDL (efect protector asupra vaselor) (Steinberg et al, 1989).

Rol central în fiziopatologia aterosclerozei, progresia și ruptura plăcii de aterom.

Terapia antioxidantă NU și-a demonstrat efectul protector decât la pacienții cu risc cardiovascular crescut.
Oxidized LDL uptake by macrophages

Native LDL → Oxidize → ox-LDL

- Native LDL-R (down regulated)
- SR-A, CD36, LOX-1 and other ox-LDL receptors (not down regulated)

Macrophage → cholesterol accumulation → Foam-cell

Endothelial cells

Smooth muscle cells

Liu et al, 2017
LOX-1: lectin-type oxidized LDL receptor

- Ox-LDL uptake by LOX-1 on endothelium
- Increase in expression of adhesion molecules and decrease in eNOS activity
- Foam cell formation mediated by SRA, CD36, LOX-1
- Stimulation of collagen synthesis and SMC proliferation
- Rupture of plaque and thrombus formation

Leiva et al, 2015
LOX-1

- Transmembrane GP
- **Soluble LOX-1**
- Undetectable under physiological conditions (host defense)
- Significantly upregulated under atherogenic conditions (binding of proatherogenic materials), inflammation, obesity, diabetes
- **MARKER for atherosclerosis risk evaluation**
- Potent TARGET for atherosclerosis prevention/therapy
LOX-1 and inflammation

1. Endothelial Dysfunction
   - ET-1
   - All
   - oxLDL
   - EC LOX-1
   - oxLDL uptake

2. Initiation
   - LOX-1 receptor + oxLDL
   - VCAM
   - ICAM

3. Progression
   - MCP-1
   - Foam Cell Formation
   - Platelet Adhesion
   - ROS
   - NO
   - MMP activity
   - EC and SMC apoptosis

4. Plaque Destabilization & Rupture
   - Platelet Adhesion
   - Leukocyte Adhesion & Transmigration
   - Chemoattractant Chemokine
   - Oxidative Stress
   - EC & SMC Apoptosis

EC LOX-1 up-regulation
- eNOS Expression
- ROS
- NF-κB

All
- ET-1
- TNF
- Shear Stress
- Diabetes

Platelets
- Apoptotic Cells
- Bacteria
- AGE


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# Pro-atherogenic effects of oxidized LDL

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<th>Stage of atherosclerotic plaque formation</th>
<th>Involvement of oxidized LDL (LDLox)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endothelial dysfunction</strong></td>
<td>- Activates the endothelial cells through the induction of adhesion molecules (ICAM, VCAM), increasing the adhesive properties of the endothelium</td>
</tr>
<tr>
<td></td>
<td>- Inhibits endothelial NO production (due to the increase of oxidative stress, producing large amounts of superoxide able to inactivate NO resulting peroxynitrite); LOX1 overexpression in the atherosclerotic plaque, associated with an impaired NO production</td>
</tr>
<tr>
<td></td>
<td>- Induces apoptosis of endothelial cells and macrophages; enables erosion of the atherosclerotic plaque</td>
</tr>
<tr>
<td><strong>Chemotactic effect</strong></td>
<td>- Stimulates secretion of chemotactic factors for monocytes, enabling recruitment of monocytes in the endothelial wall</td>
</tr>
<tr>
<td></td>
<td>- May have a chemotactic effect for monocytes, macrophages and T lymphocytes</td>
</tr>
<tr>
<td><strong>Foam cell formation</strong></td>
<td>- Capture of LDLox by the SRAI/II and SRBI; SR are not down regulated by LDL increase</td>
</tr>
<tr>
<td></td>
<td>- Induce the expression of genes associated with inflammation in macrophages</td>
</tr>
<tr>
<td></td>
<td>- Activation of macrophages, releasing proinflammatory cytokines: IL-1, TNF alpha; ROS and metalloproteases, associated with progression of inflammation</td>
</tr>
<tr>
<td></td>
<td>- ± apoptosis or necrosis of foam cells may occur due to loading with LDLox, contributing to inflammation progression</td>
</tr>
<tr>
<td><strong>Migration and proliferation of smooth muscle cells</strong></td>
<td>- Stimulated by increasing the expression of PDGF and basic fibroblast growth factor from endothelial cells and macrophages</td>
</tr>
<tr>
<td></td>
<td>- Induces the secretion of several growth factors: insulin-like growth factor and epidermal growth factor with mitogenic effect</td>
</tr>
<tr>
<td><strong>Platelets adhesion and aggregation</strong></td>
<td>- Increased prostaglandins production and platelet adhesion (Maiolino et al, 2013)</td>
</tr>
<tr>
<td></td>
<td>- CD36 is expressed in resting platelets and its interaction with LDLox enables platelet activation (Podrez et al, 2007)</td>
</tr>
</tbody>
</table>
Gargiulo et al, 2016
## Endothelial dysfunction

<table>
<thead>
<tr>
<th>Normal ENDOTHELIAL cells</th>
<th>Activated (inflammation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impermeable to large molecules</td>
<td>Increased permeability</td>
</tr>
<tr>
<td><strong>Antiinflammatory effect, resistant to leucocyte adhesion</strong></td>
<td>PROinflammatory effect: increased cytokines and adhesion molecules</td>
</tr>
<tr>
<td>Vasodilation: NO, prostacyclins</td>
<td>Reduction of vasodilating molecules</td>
</tr>
<tr>
<td>Resistance to thrombosis</td>
<td>Prothrombotic effect</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Normal SMOOTH MUSCLE CELLS</th>
<th>Activated (inflammation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal contractil function</td>
<td></td>
</tr>
<tr>
<td>Synthesis of the extracellular matrix</td>
<td>Increased synthesis of the extracellular matrix</td>
</tr>
<tr>
<td>Presence in the vascular MEDIA</td>
<td>Migration and proliferation in the vascular INTIMA</td>
</tr>
</tbody>
</table>
Pro-atherogenic effects of oxidized LDL

Gradinaru et al, 2015
The role of oxidized LDL in endothelial dysfunction

Leiva et al, 2015
**TRPV4 calcium-permeable channel is a novel regulator of oxidized LDL-induced macrophage foam cell formation**

- TRPV4: mechanosensor; ion channel in the vanilloid family
- Genetic ablation of TRPV4/ pharmacologic inhibition of TRPV4 activity (by a specific antagonist) blocked oxLDL-induced macrophage foam cell formation
- TRPV4 deficiency prevented oxLDL-induced foam cell formation
- Lack of foam cell formation in TRPV4 null cells was not due to lack of expression of CD36, a major receptor for oxLDL
- TRPV4 channel activity regulated oxLDL uptake but not its binding on macrophages

Goswami et al, 2017
The role of oxidized LDL in smooth muscle cells migration and proliferation

Leiva et al, 2015
Oxidized LDL and the pro-atherogenic effect of platelets
Signal cascade involved in oxLDL-induced endothelial cell injuries
Proinflammatory effect of oxLDL

oxLDL

- Endothelial cells
- T cells
- Adhesion molecules
- Growth factors (MCSF)
- Recruitment of leukocytes
MCP-1

- **Endothelial cells**, sensing the presence of the oxLDL, secrete the monocyte chemoattractant protein (MCP-1)
- interaction with platelet-activating factor (PAF) receptors or related receptors enables formation of MCP-1
Gene expression induced by mmLDL, oxLDL, and LPS. LDL binds to the LDL receptor as well as an undefined G protein–coupled receptor. mmLDL activates the transcription factors Egr-1, NF-AT, and PPARα and induces expression of the pro-atherogenic genes IL-8, MCP-1, and TF. OxLDL binds to the scavenger receptors SR-BI and CD36.
Possible mechanisms for removal of oxidized LDL. Circulating immune complexes containing oxidized LDL and antibodies activate complement resulting in binding of fragments of complement factor 3 (C3b).
oxLDL

- Inflammatory response
- Stimulation of SMCs
- LP retention
- Inhibition of NO synthase
Tanshinone II-A
Curcumin
Berberine
Epigallocatechin gallate
Resveratrol

Inhibition

Testosterone

Ox-LDL
LOX-1

NFKB
eNOS
Mitochondria
Cholesterol

Cytokines
NO
Caspases
Lipid Droplets

Inflammation
Endothelial dysfunction
Apoptosis
Foam cell formation

Gao et al, 2013
Oxidized cholesteryl esters and inflammation☆

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b Baker IDI Heart and Diabetes Institute, Melbourne, VIC 3004, Australia
Oxidized cholesteryl esters and inflammation

New therapies for ATS

Choi et al, 2016
Minimally oxidized LDL inhibits macrophage selective cholesteryl ester uptake and native LDL-induced foam cell formation

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- LDL oxidation necessary for foam cell formation
- Oxidized LDL contains bioactive and cytotoxic substances causing an inflammatory reaction
- Oxidized LDL inhibits the capture of cholesterol, impairing foam cell formation in macrophages treated with oxidized LDL
Assessment of oxidized LDL

- Immunoenzymatic method/ELISA
- Patient preparation: the ingestion of polyunsaturated fatty acids should be restricted before blood collection (margarine, sunflower oil)
- Normal values: less than 235 ng/ml
- High values in patients with coronary heart disease, associated with disease severity (Ehara et al, 2001; Meisinger et al, 2005)
- Predictor of cardiovascular events (Meisinger et al, 2012)

- ELISA:
- Antibodies: ox-LDL-4E6, ox-LDL-E06, ox-LDL-DLH3
Oxidized LDL, Lipoprotein (a), and Other Emergent Risk Factors in Acute Myocardial Infarction (FORTIAM Study)

Miquel Gómez, Vicente Valle, Fernando Arós, Ginés Sanz, Joan Sala, Miquel Fiol, Jordi Bruguera, Roberto Elosua, Lluís Molina, Helena Martí, M. Isabel Covas, Andrés Rodríguez-Llorián, Montserrat Fitó, Miguel A. Suárez-Pinilla, Rocío Amezaga, and Jaume Marrugat, on behalf of the FORTIAM group of researchers

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Servicio de Cardiología, Hospital Clínico Universitario, Zaragoza, Spain
Oxidized LDL, lipoprotein (a), and other emerging risk factors

FORTIAM study (Factores Ocultos de Riesgo Tras un Infarto de Miocardio): 1,371 patients with acute MI in the first 24 hours after onset

Laboratory tests:
Lp(a)
Oxidized LDL

Results: Lp(a)>60 mg/dl and oxidized LDL>74 U/l are associated with an unfavorable prognosis, regardless of cardiovascular risk factors (Gomez et al, 2009)
Oxidized LDL levels are positively related to severity of acute coronary syndromes

## Oxidized LDL and coronary heart disease: YES

<table>
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<th>Nr. patients</th>
<th>Endpoint</th>
<th>Conclusions</th>
<th>Reference</th>
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<tbody>
<tr>
<td>425 selective ACS patients followed 3-5 years</td>
<td>acute myocardial infarction (AMI) or death</td>
<td>The combined use of Ox-LDL and hs-CRP may improve prognosis after ACS with high-sensitivity and specificity.</td>
<td>Zhang et al, 2014</td>
</tr>
<tr>
<td>4782 individuals aged between 25 and 74 years (the REGICOR study)</td>
<td>fatal and non-fatal acute myocardial infarction and angina</td>
<td>OxLDL was independently associated with 10-year CAD events but not subclinical atherosclerosis in a general population</td>
<td>Gomez et al, 2014</td>
</tr>
<tr>
<td>128 consecutive angiographically proven young CAD patients (aged ⩽ 55 years) and 132 age-matched non-CAD individuals</td>
<td>Framingham risk score (FRS) and absolute 10-year CAD events risk</td>
<td>Ox-LDL is an important independent risk factor for CAD in young patients after adjusting other risk factors such as smoking, TG, and ApoB/ApoA1</td>
<td>Huang et al, 2011</td>
</tr>
<tr>
<td>284 participants: CHD±diabetes mellitus and healthy control group</td>
<td>characteristics of coronary artery lesions in CHD patients with or without hyperglycemia</td>
<td>Higher oxLDL levels may predict denoting diffuse, severe or multivessel disease in CHD patients with hyperglycemia</td>
<td>Lu et al, 2008</td>
</tr>
<tr>
<td>238 patients with documented CAD</td>
<td>cardiac death, nonfatal myocardial infarction and refractory angina requiring revascularization.</td>
<td>Measurement of circulating oxLDL may predict future CE in patients with CAD.</td>
<td>Shimada et al, 2004</td>
</tr>
</tbody>
</table>
Biomarkers to predict clinical progression in small vessel disease strokes: Prognostic role of albuminuria and oxidized LDL cholesterol

Elisa Cuadrado-Godia*, Angel Ois, Eva Garcia-Ramallo, Eva Giralt, Sara Jimena, Miguel Angel Rubio, Ana Rodríguez-Campello, Jordi Jiménez-Conde, Jaume Roquer

Neurology Department, Neurovascular Research, Program of Research on Inflammatory and Cardiovascular Disorders, Municipal Institute for Medical Research (IMIM-Hospital del Mar), Passeig Marítim 25-29, 08003 Barcelona, Spain
Biomarkers to predict clinical progression in stroke. Prognostic role of albuminuria and oxidized LDL

- 127 stroke patients in the first 6 months
- Albuminuria, von Willebrand factor and oxidized LDL were assessed
- Monitoring: 90 days
- Albuminuria and oxidized LDL are associated with an increased risk of unfavorable evolution

Cuadrado-Godia et al, 2011
<table>
<thead>
<tr>
<th>Nr. patients</th>
<th>Marker of subclinical atherosclerosis</th>
<th>Conclusions</th>
<th>References</th>
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<tr>
<td>181 patients with acute ischemic stroke</td>
<td>carotid ultrasound</td>
<td>Ox-LDL could be used in screening for vulnerable carotid plaque in clinical practice</td>
<td>Fang et al, 2011</td>
</tr>
<tr>
<td>a sample of the general middle- and old-age population of Burgos (Spain)</td>
<td>carotid artery intima-media thickness (cIMT)</td>
<td>The findings underscore the role of oxLDL in early atherosclerosis represented by the cIMT especially in older asymptomatic individuals</td>
<td>Calmarza et al, 2014</td>
</tr>
<tr>
<td>175 clinically healthy subjects, aged 40-70 years</td>
<td>carotid intima-media thickness (IMT) and augmentation index (AIx)</td>
<td>OxLDL and older age are important determinants of structural changes of the arteries in asymptomatic persons</td>
<td>Kampus et al, 2007</td>
</tr>
<tr>
<td>326 healthy men 58 years old</td>
<td>carotid artery intima-media thickness</td>
<td>OxLDL was associated with the silent phase of atherosclerosis progression in clinically healthy men independently of conventional risk factors</td>
<td>Wallenfeldt et al, 2004</td>
</tr>
<tr>
<td>214 middle-aged men from Southern Finland</td>
<td>carotid artery intima-media thickness (IMT)</td>
<td>OxLDL measured directly from plasma is independently associated with subclinical carotid artery atherosclerosis in middle-aged men</td>
<td>Metso et al, 2004</td>
</tr>
</tbody>
</table>
Arterial stiffness

Normal artery

Pathological artery

Dysfunctional endothelium

Increased collagen deposition, increased AGEs accumulation, decreased elastin content and functionality

Media

Adventitia

Increased intimal thickening

Fleenor et al, 2015
# Oxidized LDL and arterial stiffness

<table>
<thead>
<tr>
<th>Nr. patients</th>
<th>Analysed BIOMARKER of oxidative stress</th>
<th>Results</th>
<th>Authors</th>
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<tr>
<td>42 men with symptomatic peripheral arterial disease (PAD) and 46 healthy men</td>
<td>Oxidized LDL</td>
<td>PWV was associated with oxidized LDL in patients with PAD, and with both pyruvate and oxidized LDL in the control group.</td>
<td>Zagura et al, 2015</td>
</tr>
<tr>
<td>2.295 participants from the Health, Aging and Body Composition study</td>
<td>Oxidized LDL</td>
<td>High oxidized LDL levels are associated with elevated arterial stiffness in elderly patients, regardless of cardiovascular risk factors, suggesting that oxidized LDL is involved in the pathophysiology of arterial stiffness.</td>
<td>Brinkley et al, 2009</td>
</tr>
</tbody>
</table>
Oxidized HDL and LDL in adolescents with type 2 diabetes compared to normal weight and obese peers

Monica T. Marin a, Paul S. Dasari a, Jeanie B. Tryggestad a, Christopher E. Aston b, April M. Teague a, Kevin R. Short a,*

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b Pediatrics, Biomedical and Behavioral Methodology Core, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

Adolescents (11-18 years):
- 37 normal weight
- 38 obese
- 42 with type 2 DM

Laboratory investigations:
HDL, LDL, oxidized HDL, oxidized LDL, MPO
Oxidized HDL and LDL in adolescents with type 2 diabetes compared to normal weight and obese peers

Marin et al, 2015
Does oxidized LDL contribute to atherosclerotic plaque formation and microvascular complications in patients with type 1 diabetes?

Malgorzata Wegner\textsuperscript{a,*}, Maria Piorunskas-Stolzmann\textsuperscript{a}, Aleksandra Araszkiewicz\textsuperscript{b}, Dorota Zozulsinska-Ziolkiewicz\textsuperscript{b}, Dariusz Naskret\textsuperscript{b}, Aleksandra Uruska\textsuperscript{b}, Bogna Wierusz-Wysocka\textsuperscript{b}

\textsuperscript{a} Lipid Metabolism Laboratory, Department of General Chemistry, Chemistry and Clinical Biochemistry, Poznan University of Medical Sciences, Poland
\textsuperscript{b} Department of Internal Medicine and Diabetology, Poznan University of Medical Sciences, Poland
Does oxidized LDL contribute to atherosclerotic plaque formation and microvascular complications in patients with type 1 diabetes?

70 patients with type 1 diabetes mellitus examined at 2 years intervals

Intima media thickness (IMT) increased, oxidized LDL decreased! - Accumulation of oxidized LDL in the subendothelial space. Synthesis of antibodies against oxidized LDL?

Oxidized LDL influences IMT

Patients with chronic microvascular complications have higher IMT values

Conclusions: oxidized LDL accelerates atherosclerotic plaque formation and enable microvascular complications in type 1 diabetes mellitus

Wegner et al, 2012
Determinants and clinical significance of plasma oxidized LDLs in older individuals. A 9 years follow-up study

Giovanni Zuliani a,⁎, Mario Luca Morieri a, Stefano Volpato a, Giovanni B. Vigna a, Cristina Bosi Tch a, Marcello Maggio b, Antonio Cherubini c,⁎⁎, Stefania Bandinelli d,⁎⁎⁎, Jack M. Guralnik f, Luigi Ferrucci f

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⁎⁎ Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, NIH, Baltimore, MD, USA
⁎⁎⁎ Geriatric Hospital, IRCCS - Italian National Centres of Aging (INRCA), Ancona, Italy
Determinants and clinical significance of plasma oxidized LDLs in older individuals. A 9-year follow-up study.

1025 elderly patients, mean age: 75.5 years from "Invecchiare in Chianti" study

Laboratory investigations: LDL, HDL, TG, oxidized LDL, beta caroten

Monitoring: 9 years; evaluation at 3, 6 and 9 years

End-point: Cardio-vascular morbidity and mortality

Conclusions:

LDL, TG, HDL are the most important determinants of oxidized LDL, suggesting an association between small dense LDL and LDL oxidation

After 65 years, oxidized LDL decreases despite an increase of oxidative stress, due to LDL decrease

NO association was found between oxidized LDL and 9 year cardiovascular mortality and morbidity in elderly patients
Reactive oxygen species generation in peripheral blood monocytes and oxidized LDL are increased in hyperlipidemic patients

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Available online 23 May 2009
Reactive oxygen species generation in peripheral blood monocytes and oxidized LDL are increased in hyperlipidemic patients

- 14 patients with HYPERcholesterolemia
- 15 patients with combined HYPERlipidemia
- 18 patients with normal serum lipids

Assessed:
- ROS
- Oxidized LDL

Vasconcelos et al, 2009
Reactive oxygen species generation in peripheral blood monocytes and oxidized LDL are increased in hyperlipidemic patients
How do we reduce oxidized LDL?
<table>
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<th>Study group</th>
<th>Methodology</th>
<th>Results, conclusions</th>
<th>Authors</th>
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<tr>
<td>HUVECs (endothelial cells from the human umbilical vein)</td>
<td>Study of the effect of <strong>CAPSAICINE</strong> in red, hot pepper on HUVECs stimulated by oxidized LDL</td>
<td><strong>Capsaicine reduces LDL oxidation,</strong> demonstrating a protective effect against oxidative stress</td>
<td>Chen et al, 2015</td>
</tr>
<tr>
<td>38 healthy volunteers</td>
<td>Daily consumption of 300 g <strong>red or black cabbage</strong>, for 2 weeks</td>
<td>Decrease of total, LDL and oxidized LDL, glycemia</td>
<td>Bacchetti et al, 2014</td>
</tr>
<tr>
<td>81 patients with type 2 diabetes mellitus</td>
<td>Consumption of <strong>broccoli</strong> powder: 10 or 5 g/day or placebo, for 4 weeks</td>
<td>TG, oxidized LDL/LDL, plasma atherogenicity index (log TG/HDL) were significantly decreased in patients from the first group, and HDL significantly increased after 4 weeks</td>
<td>Bahadoran et al, 2012</td>
</tr>
<tr>
<td>200 healthy men</td>
<td>Consumption of <strong>olive oil</strong>, 25 ml/day, with high, medium or low phenol content</td>
<td>The concentration of <strong>autoantibodies against oxidized LDL</strong> increased proportional with the phenols dose.</td>
<td>Castaner et al, 2011</td>
</tr>
</tbody>
</table>
Pistachios Increase Serum Antioxidants and Lower Serum Oxidized-LDL in Hypercholesterolemic Adults$^{1,2}$

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$^3$Department of Nutritional Sciences, $^4$Department of Biobehavioral Health, and $^5$Integrative Biosciences, The Pennsylvania State University, University Park, PA 16802
Kay et al, 2010
# Lactobacillus and oxidized LDL

<table>
<thead>
<tr>
<th>Study population</th>
<th>Study design</th>
<th>Lactobacillus</th>
<th>Results</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 volunteers (30 in the L. plantarum and 30 in the placebo group), 18-65 years HYPERcholesterolemic patients</td>
<td>controlled, randomized, double-blind trial</td>
<td>plantarum CECT 7527 CECT 7528 CECT 7529 12 weeks</td>
<td>Significant reduction of plasma total cholesterol, LDL, oxidized LDL. Biofunctionality of L. plantarum is proportional to the cardiovascular risk of the patient (better effect in patients with higher level of cholesterol)</td>
<td>Fuentes et al, 2013</td>
</tr>
<tr>
<td>Male F344 rats fed on diets containing oxLDL and L. culture</td>
<td>In vivo study</td>
<td>bulgaricus 2038, 4 weeks</td>
<td>Reduction of LDL oxidation. Stronger antioxidative ability than vitamin E.</td>
<td>Terahara et al, 2000</td>
</tr>
<tr>
<td>127 marathon runners during 3 month training period, 6 month preparation period (decreased training, increased carbohydrate intake), marathon run</td>
<td>randomized, double-blind intervention trial</td>
<td>rhamnosus GG</td>
<td>Aerobic training reduces oxLDL, but decrease of training with increased energy intake before marathon increases oxLDL</td>
<td>Valimaki et al, 2012</td>
</tr>
<tr>
<td>38 healthy patients, over 65 years old</td>
<td>cross-sectional</td>
<td>Cultivable (casei, paracasei, acidophilus, plantarum)</td>
<td>ox-LDL level is inversely proportional to the number of Lactobacilli</td>
<td>Mikelsaar et al, 2010</td>
</tr>
</tbody>
</table>
Catechins Blunt the Effects of oxLDL and its Primary Metabolite Phosphatidylcholine Hydroperoxide on Endothelial Dysfunction Through Inhibition of Oxidative Stress and Restoration of eNOS in Rats

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\textsuperscript{a}Department of Life Science, National Taiwan Normal University, Taipei; \textsuperscript{b}Department of Family Medicine, National Taiwan University Hospital and College of Medicine, Taipei; \textsuperscript{d}Department of Surgery, Mackay Memorial Hospital and Mackay Medical College, Taipei; \textsuperscript{df}Mackay Junior College of Medicine, Nursing and Management, New Taipei City; \textsuperscript{g}Division of General Surgery, Far-Eastern Memorial Hospital, New Taipei City; \textsuperscript{f}Department of Electrical Engineering, Yuan Ze University, Taoyuan City; \textsuperscript{g}Department of Cardiology, Kuang-Tien General Hospital, Taichung; Taiwan, ROC

Key Words
Catechins • PCOOH • Oxidative stress • Endothelial cells • Nitric oxide • Vasoconstriction
Resveratrol

- Downregulates LOX-1 expression (Guo et al, 2014)
- Attenuates LDL oxidation (Gao et al, 2013)
- Inhibitory effect on ox-LDL induced macrophage apoptosis (p38 MAPK phosphorylation) (Guo et al, 2014)
- Regulates apo A1 and HDL mediated efflux (Voloshyna et al, 2013)
- Reducing ROS production, activation of caspase 3 and mitochondria-mediated apoptosis (Guo et al, 2014)
- Decrease foam cell formation (Gao et al, 2013)
HDL Inhibits Oxidative Modification of LDL

- HDL Promotes Cholesterol Efflux

- HDL Inhibits Oxidation of LDL

- Monocyte

- Adhesion Molecules

- Cytokines

- Macrophage

- MCP-1

- OX-LDL

- LDL

- Foam Cell

- Endothelium

- Vessel Lumen

- Intima
Oxidized LDL and physical therapy
Effects of lifestyle modification on oxidized LDL, reactive oxygen species production and endothelial cell viability in patients with coronary artery disease

Suphot Srimahachota a, Rattiporn Wunsuwan b, Atchasai Sirintantikorn c, Chanchai Boonla b, Suttirak Chaiwongkarjohin b, Piyaratana Tosukhowong b,∗

a Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10130, Thailand
b Department of Biochemistry, Faculty of Medicine, Chulalongkorn University, Bangkok 10130, Thailand
C Laboratory Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10130, Thailand
Effects of lifestyle change on oxidized LDL

- 30 patients with coronary heart disease

Lifestyle change:
- low lipid content diet, with an increased content of antioxidants and fibers
- moderate physical activity
- stress management

Control:

Decrease:
- Cholesterol
- TG
- Oxidized LDL

Srimahachota et al, 2010
The beneficial effect of physical activity on postprandial oxidative stress.
Drugs able to reduce oxidized LDL
Effect of variable antidiabetic treatments strategy on oxidative stress markers in obese patients with T2DM

Abeer A. Alrefai, Alsayed M. Alsalamony, Sameer H. Fatani and Hala F. M. Kamel
Effects of variable antidiabetic treatments strategy on oxidative stress markers in obese patients with T2DM

Abstract

Aim: To evaluate the effect of different anti-diabetic treatment strategy on oxidative stress markers in patients with type 2 diabetes mellitus (T2DM).

Subject and methods: A total of 93 patients with T2DM treated with metformin (G1 = 25), OHA (G2 = 22), OA and insulin (G3 = 26) and insulin alone (G4 = 20). In all patients, lipid profile and glycemic indices were assessed using routine laboratory tests. MDA and Oxidized LDL were assessed using commercially available ELISA kits. Laboratory tests were performed at baseline and at a control visit after 24 weeks of treatment.

Results: A significant decrease in the levels of MDA with improvement of glycemic control was observed in the group receiving OHA in combination with insulin therapy. A similar decrease of oxLDL was observed in all diabetic subgroups with borderline significance in those receiving metformin alone. The remaining clinical and biochemical parameters were not changed during follow-up in any of the involved groups.

Conclusion: A combination therapy with insulin was more effective in glycemic control and MDA reduction in T2DM. Whereas, a significant oxLDLc reduction was observed in T2DM irrespective of categories of antidiabetic treatment or glycemic control.

Keywords: T2DM, Oxidative stress, OHA and insulin
Effects of variable antidiabetic treatments strategy on oxidative stress markers in obese patients with T2DM

- **Inclusion criteria:**
  - 93 patients with type 2 diabetes mellitus
  - Age > 30 years
  - Duration of diabetes > 5 years

- **Exclusion criteria:**
  - Pregnant and lactating female
  - Impaired renal function (MDRD < 60 ml/min)
  - Other endocrine abnormalities
  - Chronic diseases
  - Other inflammatory disorders

ALrefai et al, 2017
Effects of variable antidiabetic treatments strategy on oxidative stress markers in obese patients with T2DM

G1: 25 patients: METFORMIN
G2: 22 patients: oral hypoglycemic agents (OHA)
G3: 26 patients: OHA+insulin
G4: 20 patients: insulin

Laboratory tests:
- Glucose panel: FBG, 2HPP
- Glycemic control: HbA1C
- LIPID profile: TC, TG, LDL, HDL
- Renal function
- Oxidative stress markers: MDA, oxLDL
- Inflammatory markers: CRP
<table>
<thead>
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<th>OxLDLc1</th>
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<th>MDA1</th>
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<th>OxLDLc3</th>
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<th>MDA3</th>
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<td>p</td>
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<td>0.69</td>
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<td>-0.16</td>
<td>0.13</td>
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<td>0.12</td>
<td>0.39</td>
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<td>TC</td>
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<td>-0.09</td>
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<td>0.58</td>
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<td>TG</td>
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<td>0.19</td>
<td>0.065</td>
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<td>LDLc</td>
<td>0.03</td>
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<td>0.15</td>
<td>0.15</td>
<td>0.12</td>
<td>0.24</td>
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<td>0.99</td>
<td>0.07</td>
<td>0.52</td>
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<td>HDLc</td>
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<td>0.75</td>
<td>0.01</td>
<td>0.9</td>
<td>0.03</td>
<td>0.76</td>
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<td>0.86</td>
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<td>LDLc/HDLc</td>
<td>0.13</td>
<td>0.9</td>
<td>0.06</td>
<td>0.56</td>
<td>0.08</td>
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<td>0.55</td>
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<tr>
<td>SCreatinin</td>
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<td>0.11</td>
<td>-0.006</td>
<td>0.95</td>
<td>0.34</td>
<td>0.001</td>
<td>0.07</td>
<td>0.51</td>
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<td>Urea</td>
<td>-0.09</td>
<td>0.37</td>
<td>-0.2</td>
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<td>0.23</td>
<td>0.025</td>
<td>0.06</td>
<td>0.57</td>
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<td>CRP</td>
<td>0.26</td>
<td>0.013</td>
<td>0.04</td>
<td>0.7</td>
<td>0.02</td>
<td>0.85</td>
<td>0.19</td>
<td>0.06</td>
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Italic values are statistically significant (P < 0.05)
<table>
<thead>
<tr>
<th>Variables</th>
<th>OxLDLc1 B</th>
<th>OxLDLc1 CI</th>
<th>OxLDLc3 B</th>
<th>OxLDLc3 CI</th>
<th>P</th>
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<tbody>
<tr>
<td>Smoking</td>
<td>-0.042</td>
<td>(-452–320.9)</td>
<td>0.024</td>
<td>(-609–505)</td>
<td>0.74</td>
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<td>Gender</td>
<td>0.31</td>
<td>(103–490)</td>
<td>-0.13</td>
<td>(-458–103)</td>
<td>0.0003</td>
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<td>SBP</td>
<td>0.76</td>
<td>(7.2–22.9)</td>
<td>0.78</td>
<td>(9–32)</td>
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<td>DBP</td>
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<td>(-65–21.8)</td>
<td>-0.54</td>
<td>(-72–8)</td>
<td>0.013</td>
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<td>Neuropathy</td>
<td>-0.76</td>
<td>(-493–279)</td>
<td>0.08</td>
<td>(-395–704)</td>
<td>0.58</td>
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<tr>
<td>FBG</td>
<td>-0.15</td>
<td>(-3.9–0.51)</td>
<td>-0.059</td>
<td>(-5.7–3.1)</td>
<td>0.57</td>
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<td>PPG</td>
<td>0.26</td>
<td>(0.53–4.44)</td>
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<td>(-1.5–5.3)</td>
<td>0.28</td>
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<tr>
<td>S. creatinine</td>
<td>0.4</td>
<td>(1487–5080)</td>
<td>0.25</td>
<td>(204–534)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Table 6: Linear regression analysis to investigate independent factors associated with oxLDL in diabetic patients

ALrefai et al, 2017
HYPERglycemia

ROS production

Inflammation

Chemical modification of LP

Complications of DM

Antidiabetic drugs

THERAPY

ALrefai et al, 2017
Metformin and oxidized LDL inhibited ox-LDL-induced macrophage apoptosis and inhibits macrophage lipid uptake (Huangfu et al, 2018)

enhanced SIRT1 and AMPK expression in human umbilical vein endothelial cells (HUVECs), also inhibited oxLDL-increased LOX-1 expression and oxLDL-collapsed eNOS levels (Hung et al, 2016)
Vitamin E Reduces the Uptake of Oxidized LDL by Inhibiting CD36 Scavenger Receptor Expression in Cultured Aortic Smooth Muscle Cells

Roberta Ricciarelli, PhD; Jean-Marc Zingg, PhD; Angelo Azzi, MD

**Background**—Vitamin E is well known as an antioxidant, and numerous studies suggest that it has a preventive role in atherosclerosis, although the mechanism of action still remains unclear.

**Methods and Results**—The original aim of this study was to establish whether $\alpha$-tocopherol (the most active form of vitamin E) acts at the earliest events on the cascade of atherosclerosis progression, that of oxidized LDL (oxLDL) uptake and foam-cell formation. We show here that the CD36 scavenger receptor (a specific receptor for oxLDL) is expressed in cultured human aortic smooth muscle cells (SMCs). Treatment of SMCs and HL-60 macrophages with $\alpha$-tocopherol (50 $\mu$mol/L, a physiological concentration) downregulates CD36 expression by reducing its promoter activity. Furthermore, we find that $\alpha$-tocopherol treatment of SMCs leads to a reduction of oxLDL uptake.

**Conclusions**—This study indicates that CD36 is expressed in cultured human SMCs. In these cells, CD36 transports oxLDL into the cytosol. $\alpha$-Tocopherol inhibits oxLDL uptake by a mechanism involving downregulation of CD36 mRNA and protein expression. Therefore, the beneficial effect of $\alpha$-tocopherol against atherosclerosis can be explained, at least in part, by its effect of lowering the uptake of oxidized lipoproteins, with consequent reduction of foam cell formation. (*Circulation*. 2000;102:82-87.)
Immunofluorescence

Nuclei

CD36

control

α-tocopherol

β-tocopherol

Negative control
**Statins**

- Cholesterol lowering (inhibition of HMG-CoA reductase)
- Lowering LDL means lowering Ox-LDL (Tsai et al, 2014)
- Protective effects: endothelial function, plaque stability, anti-inflammatory effects, correction of prothrombotic tendencies

- Decrease LOX-1 expression, ox-LDL binding and uptake in endothelial cells, macrophages, monocytes, SMCs, platelets (Gao et al, 2013)
- Reduced endothelial cell apoptosis, monocyte-endothelial cell adhesion, vascular inflammation, NO production, platelet aggregation, ACE expression (Draude et al, 1999; Maron et al, 2000; Li et al, 2001; Hofnagel et al, 2006; Sun et al, 2011)

Changes in oxidized low density lipoprotein (Ox-LDL) level in the statin and non-statin groups after acute ischemic stroke.

*Tsai et al, 2014*
Testosterone

- **Anti-atherogenic**
  - Up-regulate SR-B1, cholesterol uptake in macrophages (Langer et al, 2002)
  - Inhibition of expression of LOX-1 and NF-κB → impaired pro-inflammatory signal transduction → impaired plaque development (Gao et al, 2013)
  - Regulation of LOX-1 pathway by male hormones → new anti-atherosclerotic therapies?
  - Stimulation of cellular cholesterol efflux (Eckardstein et al, 2001)

- **PRO-atherogenic:**
  - Impair FMD (Eckardstein et al, 2003)
  - Decrease of HDL (Eckardstein et al, 2003)
## Estrogens

<table>
<thead>
<tr>
<th>Study group</th>
<th>Type of estrogen</th>
<th>Conclusion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 patients with PCOS</td>
<td>Diane 35 (ethinyl-estradiol)</td>
<td>Diane-35 had a positive effect on lipid profile, increasing PON1 and decreasing ox-LDL</td>
<td>Carlioglu et al, 2014</td>
</tr>
<tr>
<td>HUAEC</td>
<td>estradiol</td>
<td>Estradiol increased the attenuated endothelial NO production induced by ox-LDL</td>
<td>Novella et al, 2013</td>
</tr>
<tr>
<td>HUVEC</td>
<td>17-beta-estradiol</td>
<td>17-beta-estradiol decreases TNF alpha and ox-LDL induced apoptosis in endothelial cells</td>
<td>Florian et al, 2008</td>
</tr>
</tbody>
</table>
Conditions associated with a high level of oxidized LDL

- Coronary heart disease
- Stroke
- Dyslipidemia: HYPERcholesterolemia, HYPERtriglyceridemia
- Increase of small, dense LDL
- Diabetes mellitus
- Systemic inflammation
- Metabolic syndrome, Central obesity
- Autoimmune conditions
Anti-Oxidized Low-Density Lipoprotein Antibodies: protection/pathogenicity?

- Immunogenic molecule that stimulate the induction of antibodies
- Correlation with the extent of atherosclerosis and cardiovascular disease: autoantibodies cross-reactive with oxLDL may provide a pathogenic mechanism for accelerated atherosclerosis (George et al, 1997)
- **PROTECTIVE:** humoral immunity to oxLDL can reduce the incidence of atherosclerosis;
- *Natural anti-oxLDL antibodies:* higher levels in healthy children than adults; the binding activity of anti-oxLDL IgG is significantly higher in children than in adults (Iughetti et al, 1999): neutralize and catabolize oxLDL (Fukumoto et al, 2000)
- anti-oxLDL antibodies were decreased in patients with borderline hypertension (Wu et al, 1999)
- a significant negative correlation between carotid IMT and anti-oxLDL antibodies in patients with rheumatoid arthritis (Nowak et al, 2016)
Conclusions: oxLDL

- is a complex mixture of chemical entities
- is an oxidative stress, atherosclerosis and cardiovascular risk marker
- is involved in several proatherogenic mechanisms related to LOX-1
- provides important prognostic information in patients with coronary heart disease, stroke, diabetes mellitus and dyslipidemia
- oxLDL level can be decreased by physical therapy, several fruits and vegetables, Lactobacillus, resveratrol, HDL, antidiabetic drugs, statins, estrogen and testosterone
- TRPV4 and LOX-1 could represent new therapeutic targets in atherosclerotic patients