

EDIC: Other risk factors for diabetic complications
Lipoproteins and other lipid molecules

*Ira Goldberg, Columbia University
College of Physicians and Surgeons,
New York NY*

Bethesda, April 10, 2003

Lipoproteins and other lipid molecules

- **Lipoproteins and atherosclerosis**
 - Humans
 - Animal models
- **Fatty acids and other lipolysis products**
 - Generation
 - Vascular effects

Why is atherosclerosis increased in patients with diabetes?

- Hyperglycemia
- Hyperinsulinemia
- Hypertension
- Lipid abnormalities

I don't know!

Hyperglycemia is not the major cause of accelerated atherosclerosis in patients with diabetes

- Correlations of glucose intolerance and macrovascular disease
- Populations with diabetes and low cholesterol - Japan
- Animal models

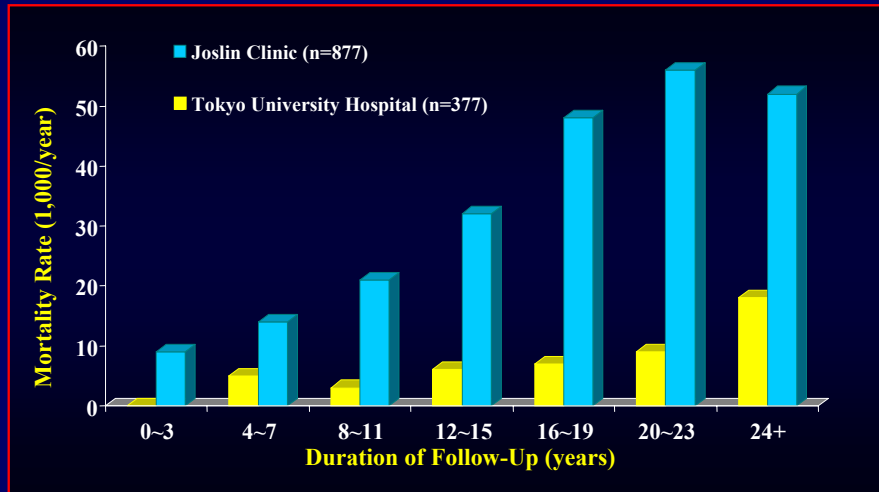
UKPDS: Order of Importance for Prediction of Coronary Artery Disease (Baseline Epidemiologic Data)

<u>Variable</u>	<u>P value</u>
1. LDL-C	<0.0001
2. HDL-C	0.0001
3. HbA _{1c}	0.0022
4. Systolic BP	0.0065
5. Smoking	0.056

N=2693 Type 2 diabetes patients

Adapted from Turner RC et al. *BMJ* 1998;316:823-828.

Coronary Heart Disease Mortality is Low in Diabetic Japanese by Direct Comparison with the Joslin Cohort



CHD mortality rate by follow-up duration in the Tokyo University and Joslin Clinic cohorts

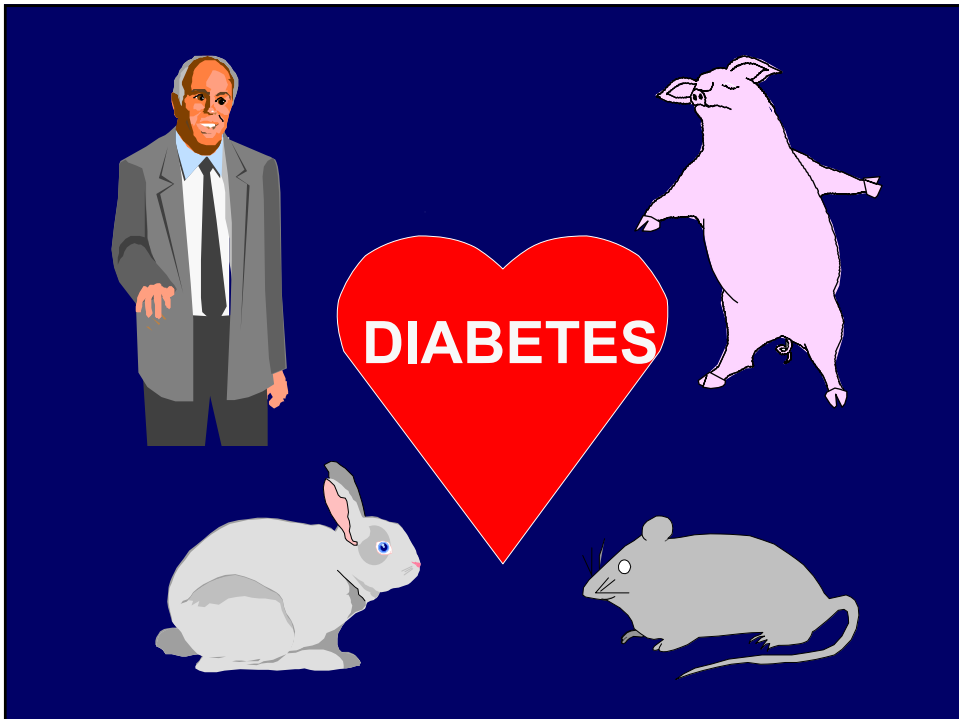
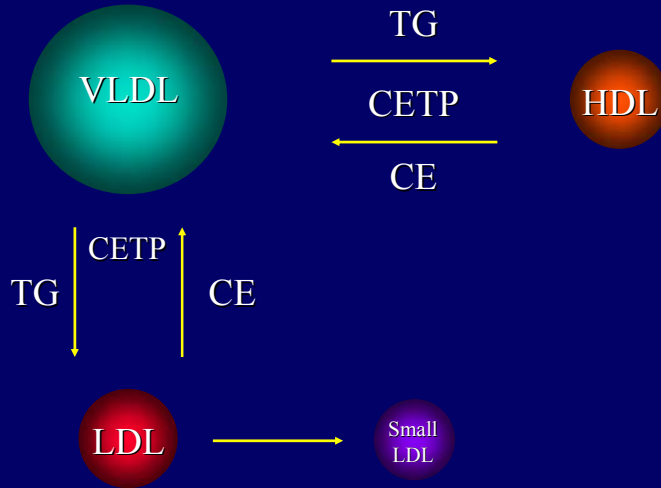
Toeko Matsumoto, MD, Nobuhiro Yamada, MD, Yasuo Ohashi, Ph.D, Masatoshi Kikuchi, MD

Diabetes Care, Volume 17, No. 9, Sept. 1994

Lipoprotein abnormalities in type 2 diabetes

- Hypertriglyceridemia
- Small Dense LDL
- Reduced HDL
- Postprandial lipemia

Plasma Lipid Exchange



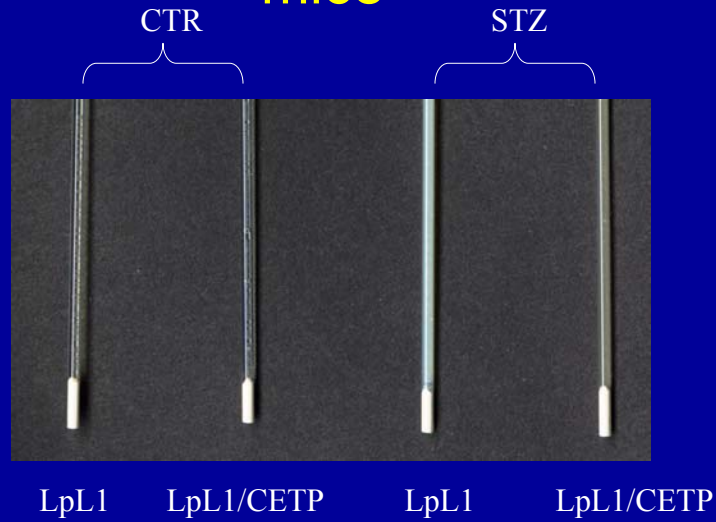
Studies of atherosclerosis in diabetic mice

- Mice strains - LeBoeuf
- LDL receptor knockout - Reaven
- ApoE knockout – Schmidt
- Human B transgenic mice – Kako
- Newer – unpublished
 - LDLr0/BalbC, viral destruction of islets

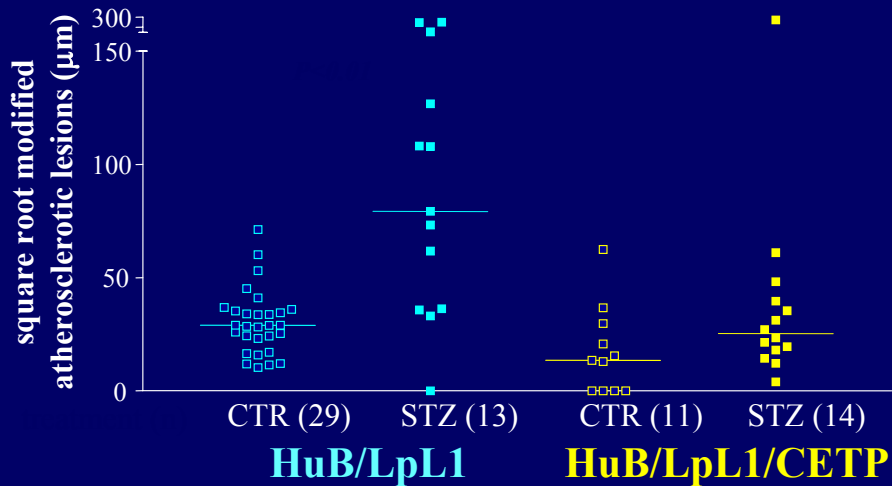
Objective: To determine if hyperglycemia will increase atherosclerosis in mice with a human-like lipoprotein profile

**HuB x LpL heterozygous
knockout x CETP**

STZ treatment led severe dyslipidemia in HuB/LpL1 mice



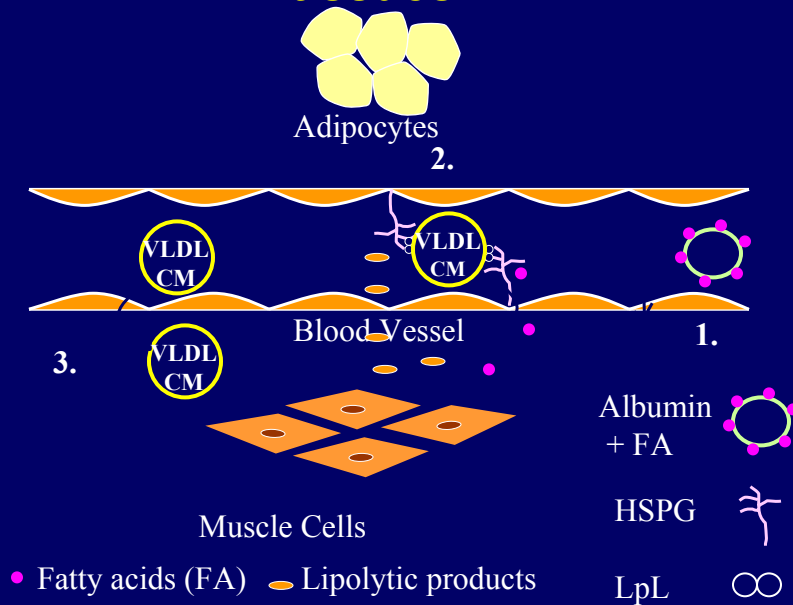
STZ treatment accelerated atherosclerosis in HuB/LpL1



Lipoproteins and other lipid molecules

- Lipoproteins and atherosclerosis
 - Humans
 - Animal models
- Fatty acids and other lipolysis products
 - Generation
 - Vascular effects

Fatty Acid Delivery to Peripheral tissues



Does lipolysis increase atherosclerosis?

Lipoprotein lipid accumulates within the artery

Arterial Accumulation of VLDL Lipids and Protein

TRITC



DiI

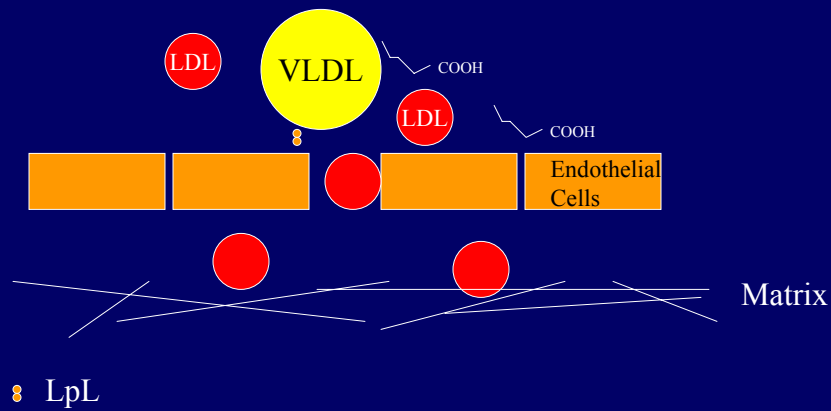


Rutledge et al. *Circ Res.* 86:768-73, 2000

Pathological effects of lipolysis

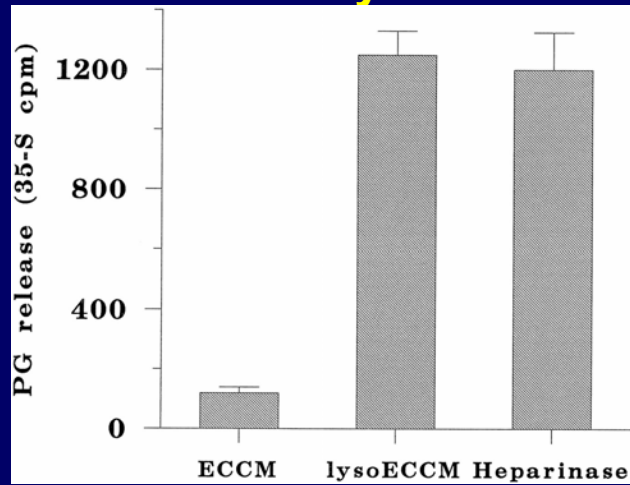
- Increases arterial wall permeability and allows greater passage of lipoproteins into the intima
- Alters vasoreactivity
- Increases expression of inflammatory molecules

Lipolysis increases endothelial permeability



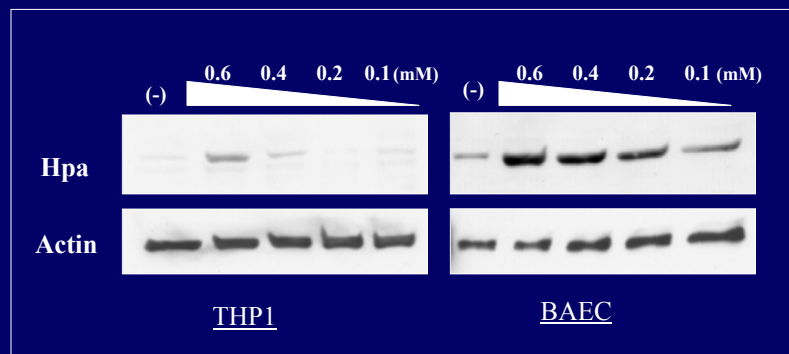
Rutledge et al. Circ Res. 80:819-828, 1997.

Lysolecithin effects on EC Production of a HSPG releasing activity



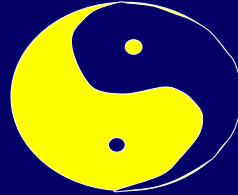
Pillarisetti et al. J Biol Chem 272:15753-15759, 1997

Oleic Acid stimulates Heparanase (Hpa) expression



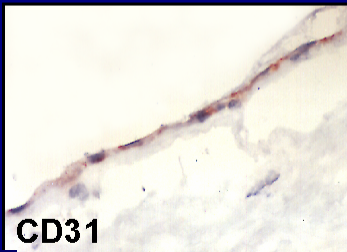
Fatty acids are natural PPAR agonists

PPAR α



- Atherosclerosis
 - Knockout mice have less atherosclerosis
 - Agonist reduce atherosclerosis?

PPAR α Expression in Endothelial Cells in Human Carotid Arteries



PPAR α also expressed in

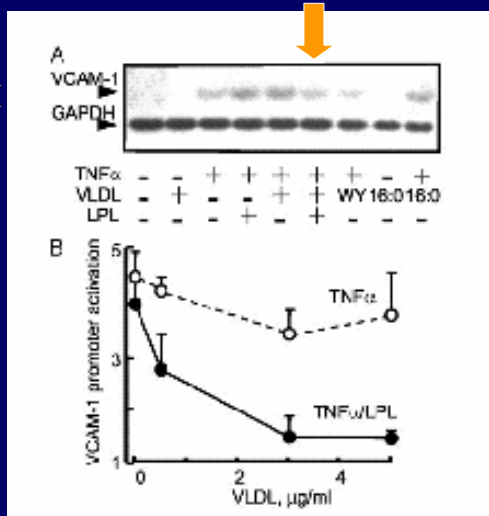
- Vascular smooth muscle cells
- Monocytes and macrophages
- T lymphocytes

Lipolysis of triglyceride-rich lipoproteins generates PPAR ligands: Evidence for an antiinflammatory role for lipoprotein lipase

Ouliana Zlotorenko^{1*}, Stephane Ferrey², Liana Asotiyani¹, Juliana Theong¹, Karen L. MacLaurin¹, David E. Moller¹, Daniel J. Rader¹, Alex Sevastian¹, Rudolf Zechner¹, Gerald Hoeller¹, and Jorge Plutzky^{1*}

VLDL+LpL decreased VCAM
And TNF production by EC

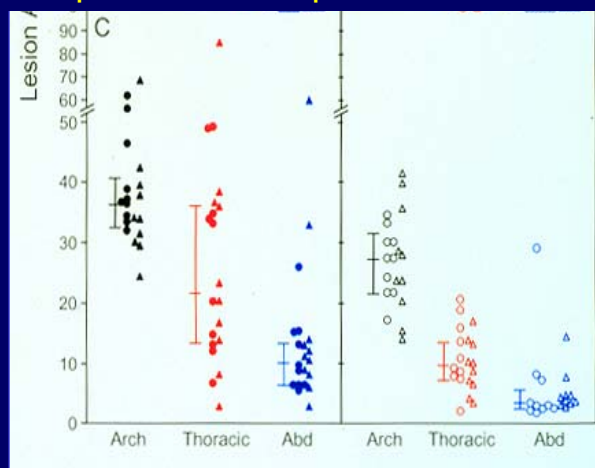
PNAS 2003, 100:2730-5



PPAR α deficiency reduces Atherosclerosis in ApoE0

ApoE0

ApoE0/ PPAR α -/-



Courtesy of C. Semenkovich. From J Clin Invest. 2001, 107:1025

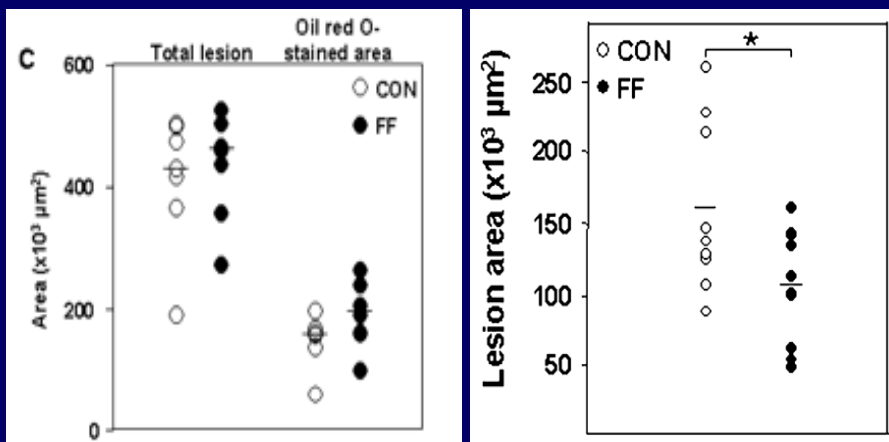
These mice also have less hypertension and less glucose intolerance, but more VLDL.

Reduction of Atherosclerosis by the Peroxisome Proliferator-activated Receptor α Agonist Fenofibrate in Mice*

BUT only when human apoAI is expressed

ApoE0

ApoE0/Human apoAI Tg



FF=fenofibrate

Lipoproteins and other lipid molecules

- **Lipoproteins and atherosclerosis**
 - Humans
 - Animal models
- **Fatty acids and other lipolysis products**
 - Generation
 - Vascular effects

Appearance of Imprinting for CAD

