Diabetic Complications

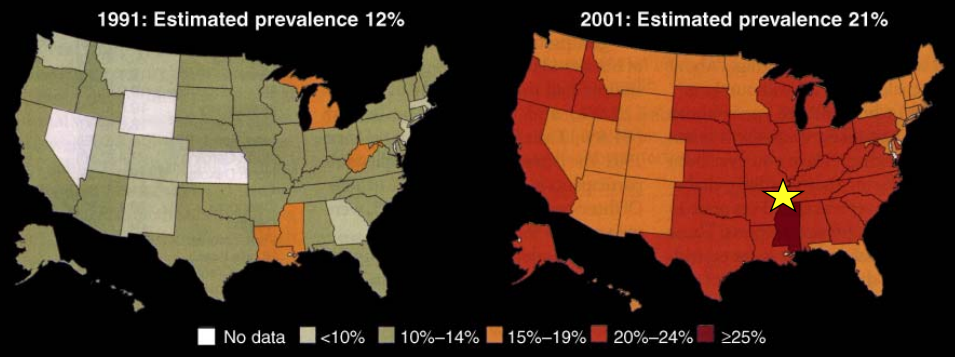
Chronic

Thomas A. Hughes, M.D.
Professor of Medicine
Division of Endocrinology, Metabolism, and Diabetes
University of Tennessee Health Science Center
(HughesEndo.com)

VBWG

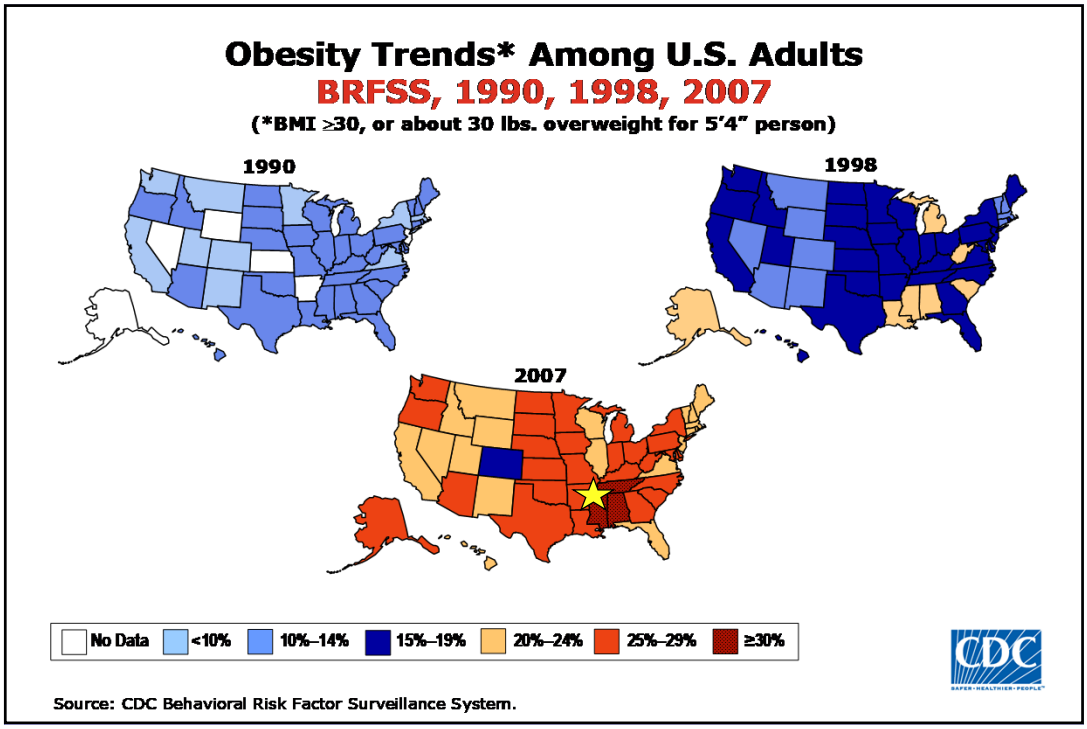
Nationwide epidemic of obesity

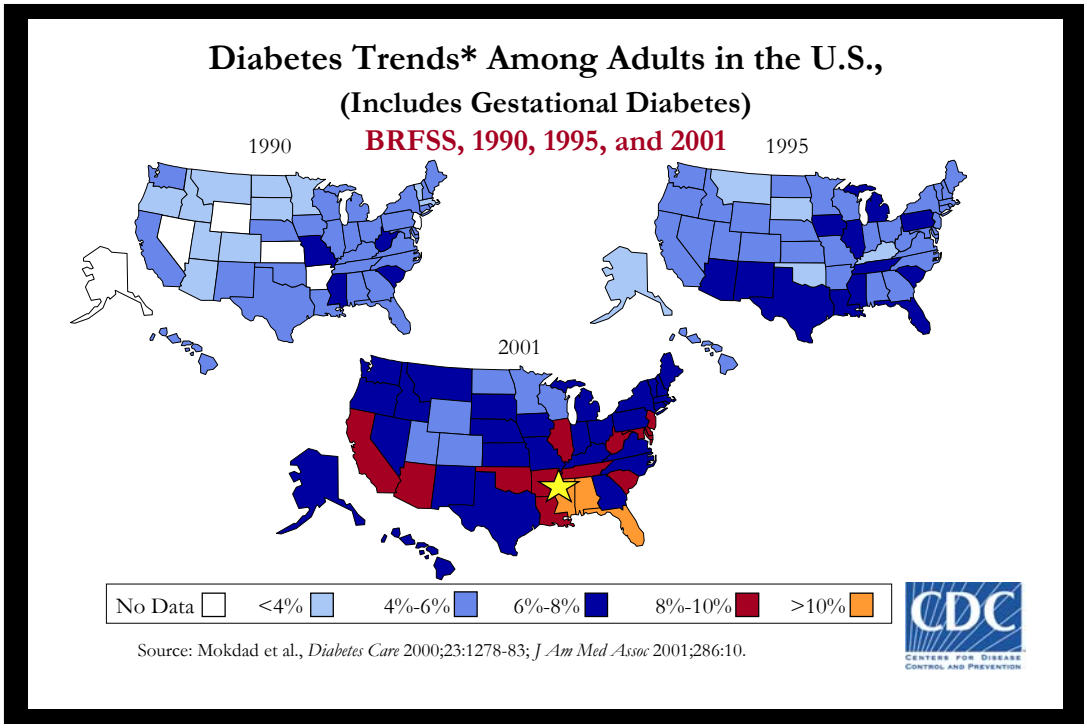
Prevalence of obesity (BMI ≥30 kg/m^2)
Telephone survey of 195,005 adults ages ≥18 years



Implications of obesity at age 40 years:
↓ lifespan of 7.1 years (women), 5.8 years (men)

Mokdad AH, et al. *JAMA*. 2003;289:76-79.
Peeters A, et al. *Ann Intern Med*. 2003;138:24-32.

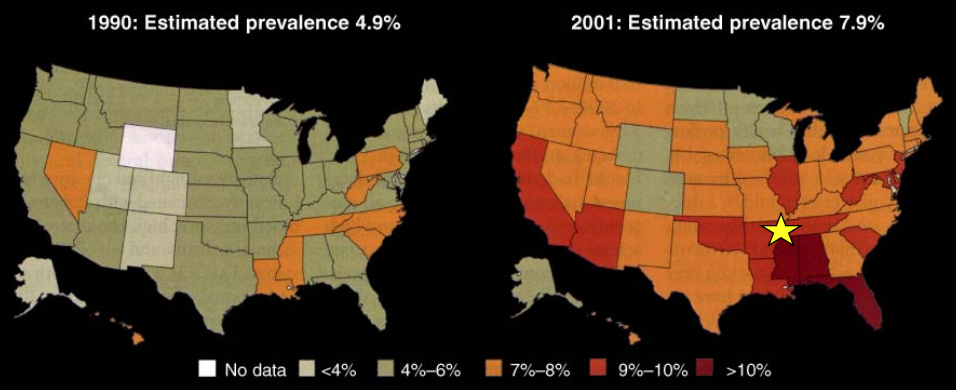

Obesity Trends* Among U.S. Adults
BRFSS, 1990, 1998, 2007
(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)
1990
1998
2007
No Data
<10%
10%–14%
15%–19%
20%–24%
25%–29%
≥30%
CDC
Source: CDC Behavioral Risk Factor Surveillance System.


Diabetes Trends* Among Adults in the U.S.,
(Includes Gestational Diabetes)
BRFSS, 1990, 1995, and 2001
1990
1995
2001
No Data
<4%
4%-6%
6%-8%
8%-10%
>10%
Source: Mokdad et al., Diabetes Care 2000;23:1278-83; J Am Med Assoc 2001;286:10.
CDC
Centers for Disease Control and Prevention

VBWG

Nationwide epidemic of diabetes

Telephone survey of 195,005 adults ages ≥18 years



Mokdad AH, et al. *JAMA*. 2003;289:76-79.

Diabetes Mellitus in the US: Overview

Prevalence

- 15.7 million Americans (5.9% of the population)
  - 10.3 million diagnosed
  - 5.4 million not diagnosed

Incidence

- 798,000 new cases diagnosed yearly
- Leading cause of
  - blindness in adults
  - end-stage renal disease
  - nontraumatic amputations
- Healthcare costs $98.2 billion annually

90% to 95% of cases are type 2 diabetes

ADA *Diabetes Care*. 1998;21:296-309.
NIDDK. Diabetes Statistics. NIH Publication No. 98-3926; November 1997 (updated February 1998).

1.1 ©1999 PPS

U.S. Diabetes Prevalence
All Ages, 2007

- 23.6 million people have diabetes

  Diagnosed: 17.9 million people
  - Type 1 diabetes accounts for 5% – 10%
  - Type 2 diabetes accounts for 90% – 95%

  Undiagnosed: 5.7 million people

  Total Cost: **$174 billion**

  Direct Medical Cost: $**116 billion**

  Indirect Cost: **$58 billion**

NIDDK, National Diabetes Statistics 2007.
www.diabetes.niddk.nih.gov/dm/pubs/statistics

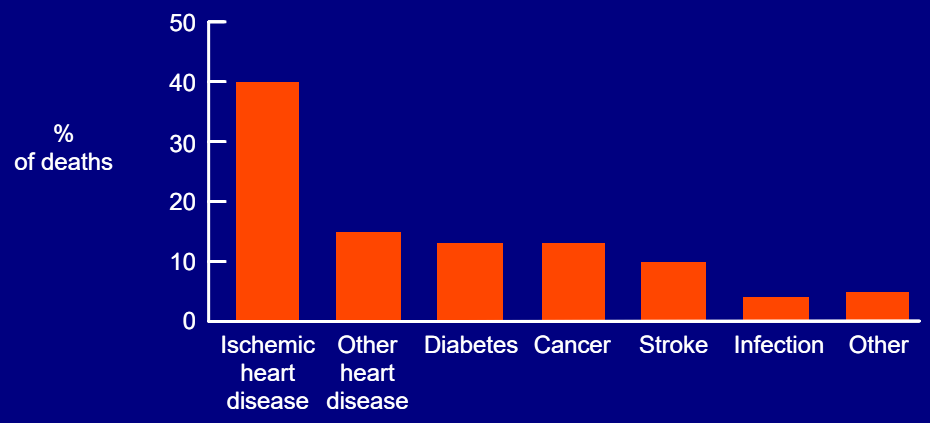
Every 24 Hours…

- 4,384 - new cases of diabetes are diagnosed
- 195 - non-traumatic lower limb amputations are performed
  - Leading cause of non-traumatic amputations (neuropathy)
- 128 - people begin treatment for renal failure
  - Leading cause of renal failure
- 50 - people go blind – Leading cause of blindness
- 839 - people die of diabetes or diabetes is a contributing cause of death

Derived from:
NIDDK, National Diabetes Statistics 2007.
www.diabetes.niddk.nih.gov/dm/pubs/statistics

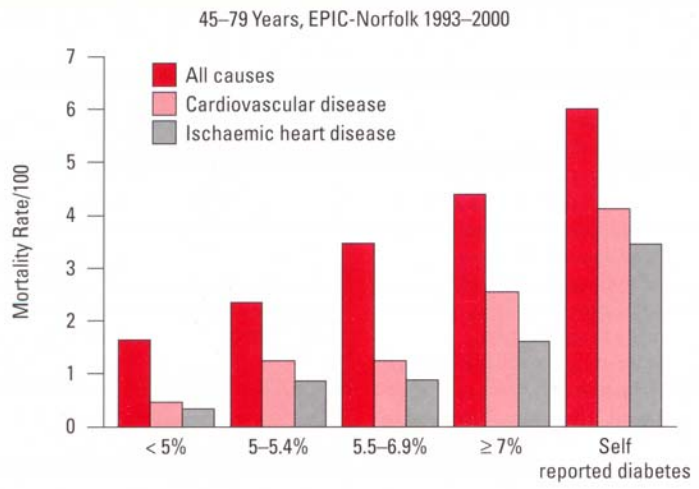
Mortality in People With Diabetes

Causes of Death



Geiss LS et al. In: *Diabetes in America*. 2nd ed. 1995;chap 11.

Figure 3.
Population Excess Mortality by Glycated Haemoglobin and Diabetes Status in Men.



Khaw et al. *BMJ*. 2001.

Atherosclerosis: Introduction

Impact of Diabetes (Types I & II) on Atherogenesis:

Metabolic - hyperglycemia, hyperinsulinemia
Chemical - glycation, oxidation

Lipoproteins, Apolipoproteins, and Lipids

Vessal Wall - cells, matrix, and contraction

Coagulation - platelets, clottings factors, and fibrinolysis

Neovascularization

Diabetic Complications

Mechanisms:

- Elevated Fatty Acids (and abnormal lipoproteins)
- Altered cytokines, signaling molecules, and hormones
- Lipid accumulation: esp - muscle, liver, islets, heart
- Oxidative Stress: NADH/NAD^+, Super Oxide, Nitric Oxide
- Inflammation: NF-kB, Prostaglandins
- Hyperglycemia
  - Glycosylation – advanced glycosylation end products
  - Inositol – DAG, phosphoinositides, IP_3
  - Sorbitol

Nitric Oxide
Adiponectin

Obesity
(Visceral)

Hyperglycemia

AT-II

FFA

TNFa

Super Oxide

NAD(P)H
Oxidase

Protein
Kinase C

NF-kB

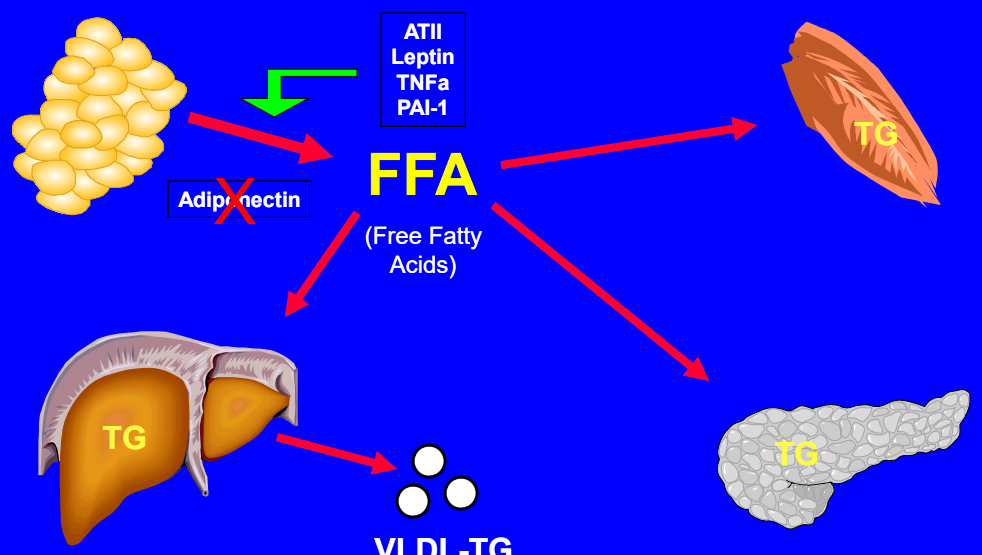
IL-1, IL-6
IL-8, MCP

Adhesion
Molecules

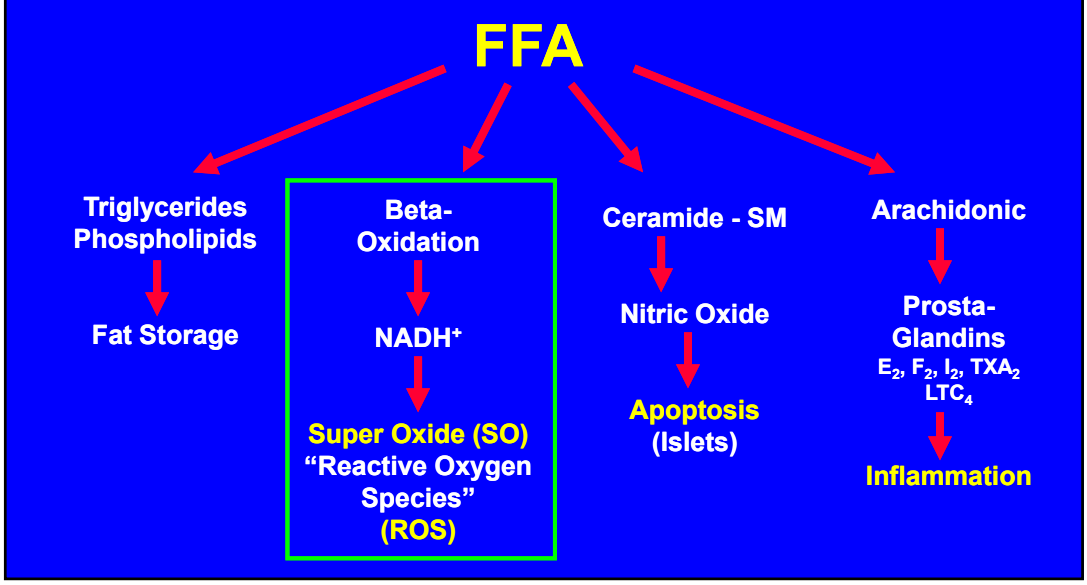
Insulin
Resistance

TGFb

Insulin Resistance Syndrome

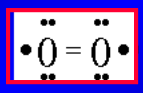


Insulin Resistance Syndrome



Atherosclerosis: LP Oxidation - Free Radicals

Oxygen:



Biradical - can accept a pair of electrons
Spin restriction of these electrons slows the reaction
This allows one-electron transfer ---> Free Radical Formation

Superoxide:

$$O_2 + e^- \longrightarrow O_2^-\bullet$$

$$O_2^-\bullet \xrightarrow{Dismutase} H_2O_2$$

Stimulated by TZDs

First intermediate in reduction of oxygen to water
Can lead to formation of many other reactive species
(hydrogen peroxide [diffusion], hydroxyl, perhydroxyl)

Catalase → H_2O

H_2O_2 → Vasc prolif & hypertrophy

Hydroxyl Radical:

$$H_2O_2 + Fe^{2+} \longrightarrow Fe^{3+} + OH^- + \bullet OH$$
$$H_2O_2 + Cu^{+} \longrightarrow Cu^{2+} + OH^- + \bullet OH$$
$$H_2O_2 + O_2^-\bullet \longrightarrow O_2 + H_2O + \bullet OH$$

Most potent oxidant
Extremely short half-life
Metals required in biol.

Atherosclerosis: LP Oxidation - Free Radicals

Biological Sources of Super Oxide (SO):

H_2O_2 Diffuses Away

- NADH oxidation in mitochondrial electron transport
- NADPH oxidation by microsomal cytochrome P-450
- Phagocytic cells: glucose/FFA --> ↑ H_2O_2 + Myeloperoxidase
  - MPX generates Free Radicals from H_2O_2

Oxidation of Organic Molecules:

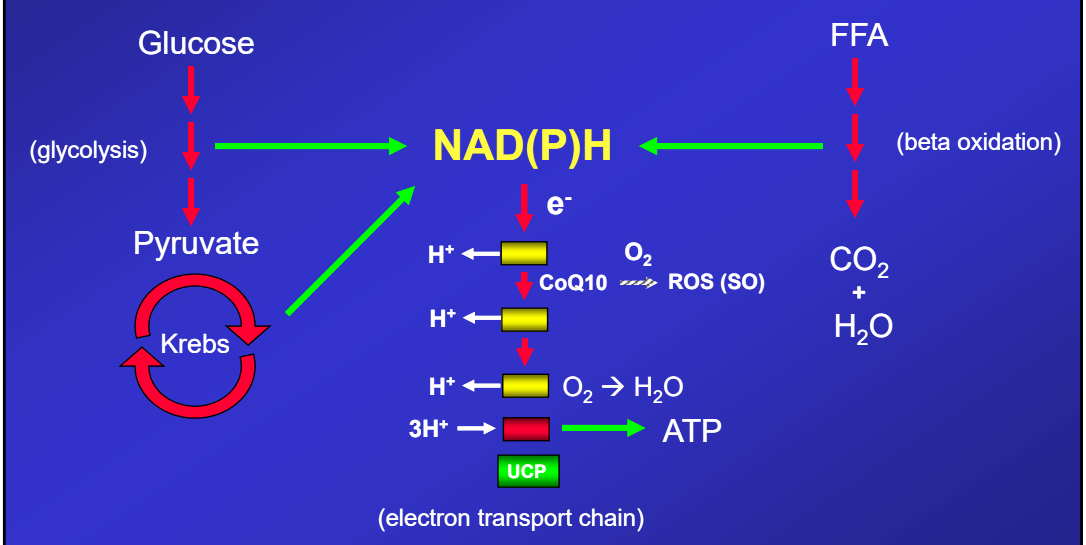
Proteins: proline; histidine, arginine (metal binders)---> fragmentation, aggregation, cross-linking, degradation

Fatty acids: linoleic (18:2), arachidonic (20:4), DHA (22:6) ---> peroxidation, aldehyde formation ---> cytotoxic, mutagenic

Carbohydrates: glucose ---> auto-oxidation

Yu BP; Physiol Reviews 74:139, 1994

Glucose and Fatty Acid Oxidation



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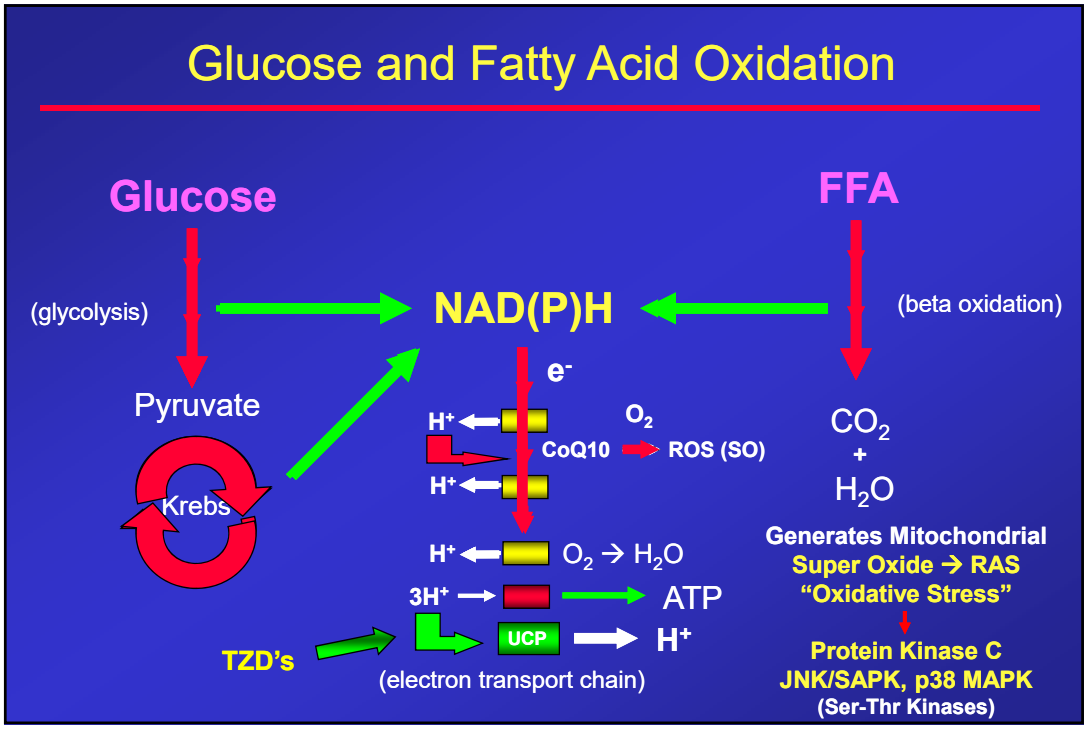
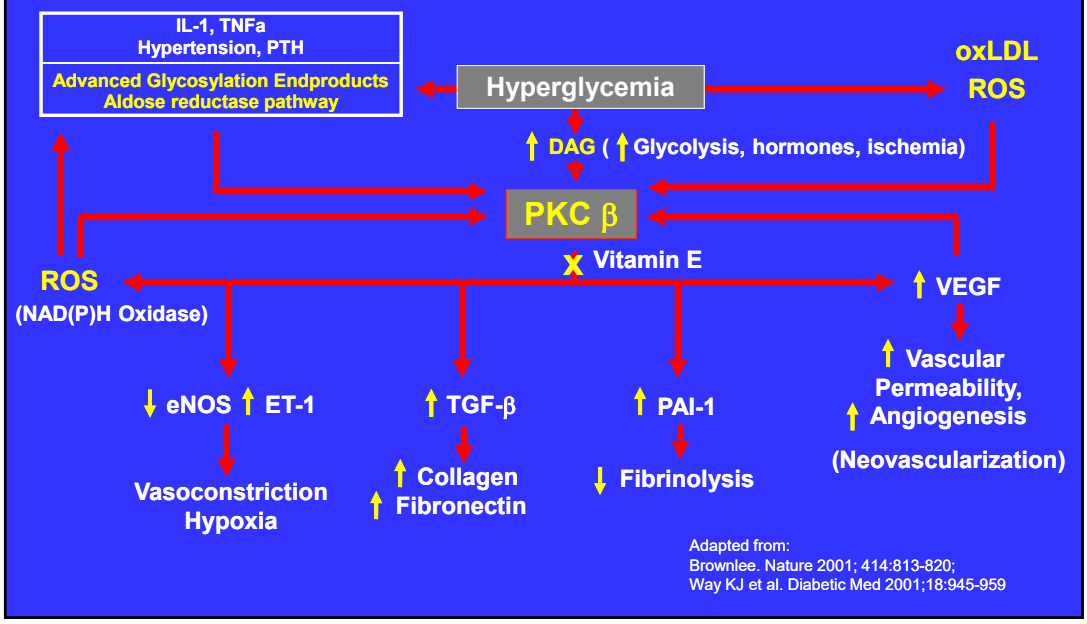


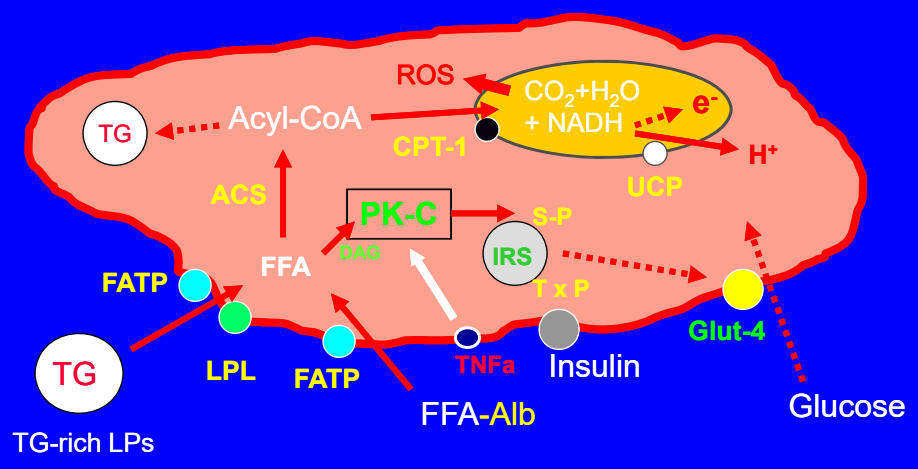
Diabetes-induced PKC β Activation



Adapted from:
Brownlee. Nature 2001; 414:813-820;
Way KJ et al. Diabetic Med 2001;18:945-959

Protein Kinase C: Muscle Insulin Resistance

Insulin Receptor Substrate (IRS) → Ser Phos blocks Tyr Phos



FFAs & TNFa induce muscle insulin resistance

Martin et al, Atheroscl Suppl S75, 1998
Fruchart et al, Curr Opin Lipidol 10:245, 1999

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auto-oxidation

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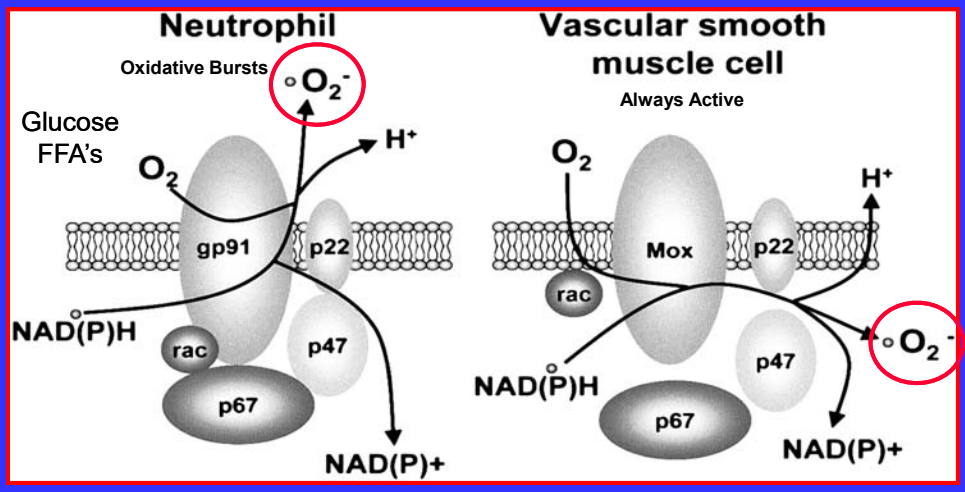
Structure of the NAD(P)H Oxidase (Nox)

Vasc Oxidase Activated by: PK-C, AT-II, TNFa, Thrombin, & Turbulent Flow
Inhibited by: Nitric Oxide - TZD's, Statins (Amlodip → scavenger)



Reprinted with permission from Griendling KK et al. *Circ Res*. 2000 86:494–501.

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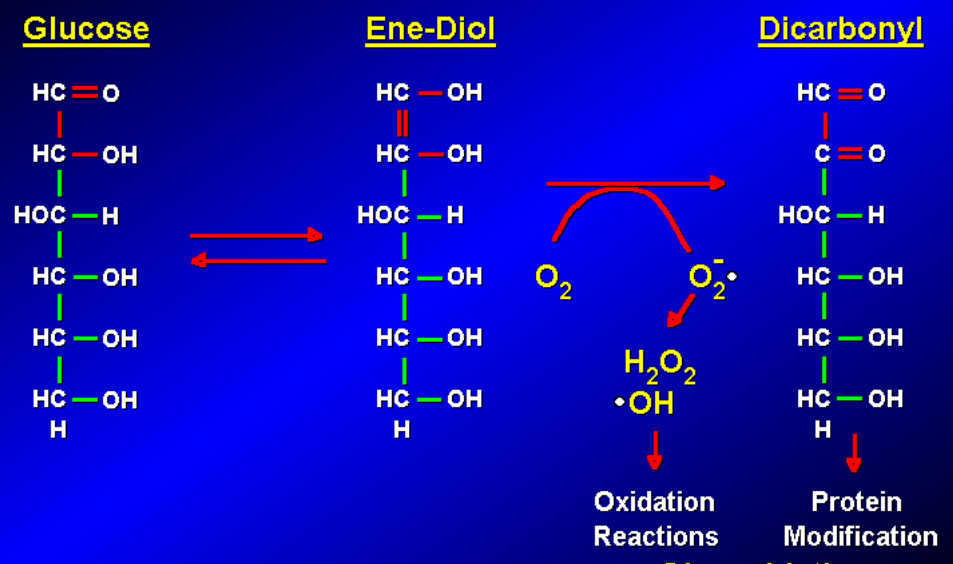
Yu BP; Physiol Reviews 74:139, 1994

Atherosclerosis: Glucose Auto-oxidation



Semenkovich and Heinecke; Diabetes 46:327, 1997

Atherosclerosis: LP Oxidation - Protection

Biological anti-oxidant systems:

Superoxide Dismutase (SOD): $O_2^-\bullet + O_2^-\bullet \xrightarrow{2H+} H_2O_2 + O_2$

Catalase: wide tissue distribution $H_2O_2 \xrightarrow{Catalase} H_2O$

GSH peroxidase: $2GSH + H_2O_2 \xrightarrow{GSH-PX} GSSG + 2H_2O$

Vitamin E: Converts SO, •OH, lipid radicals to less reactive forms
Breaks lipid peroxidation chain reaction

Beta Carotene: Scavenges SO

Vitamin C: Scavenges SO and •OH; improves vasodil in DM
Regenerates Vitamin E

Transferrin, Ceruloplasm: bind Fe and Cu

Atherosclerosis: Anti-oxidants in Diabetes

Biological anti-oxidant systems:

Superoxide Dismutase (SOD): ~↓ RBCs **Stimulated by TZDs**

Catalase: ~ RBCs

GSH peroxidase / GSH: ~↓ plasma, WBCs **Regenerated by Lipoic Acid**

Vitamin E: ~↓ plasma ↓ platelets

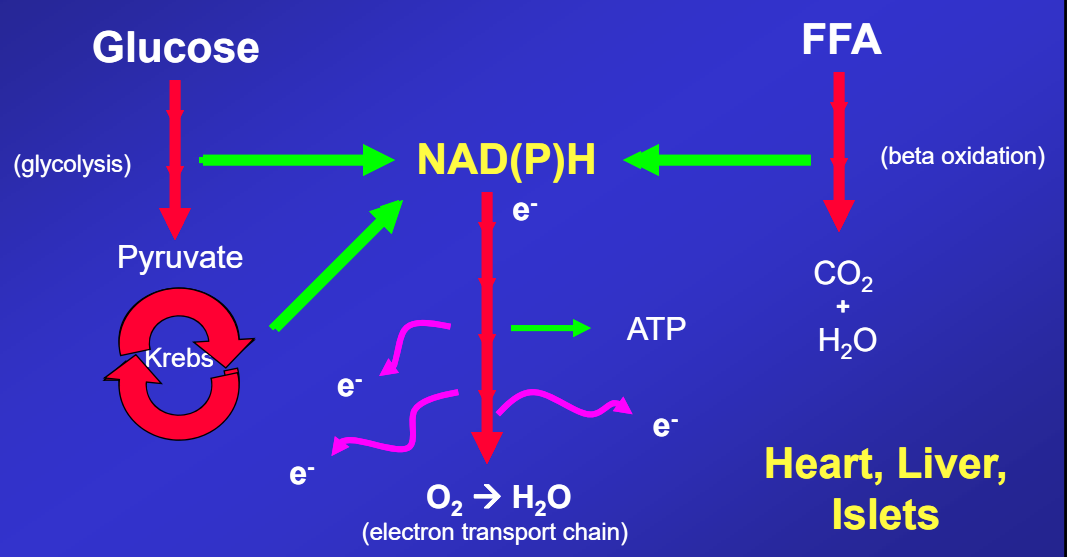
Beta Carotene:

Vitamin C: ↓ plasma ↓ monos ↑ turnover

Transferrin, Ceruloplasm: ~↑ plasma

Lyons TJ; Diabetes Med 8:411, 1991

High Oxidative Stress + Triglyceride → Cell Damage, Mutation, & Death



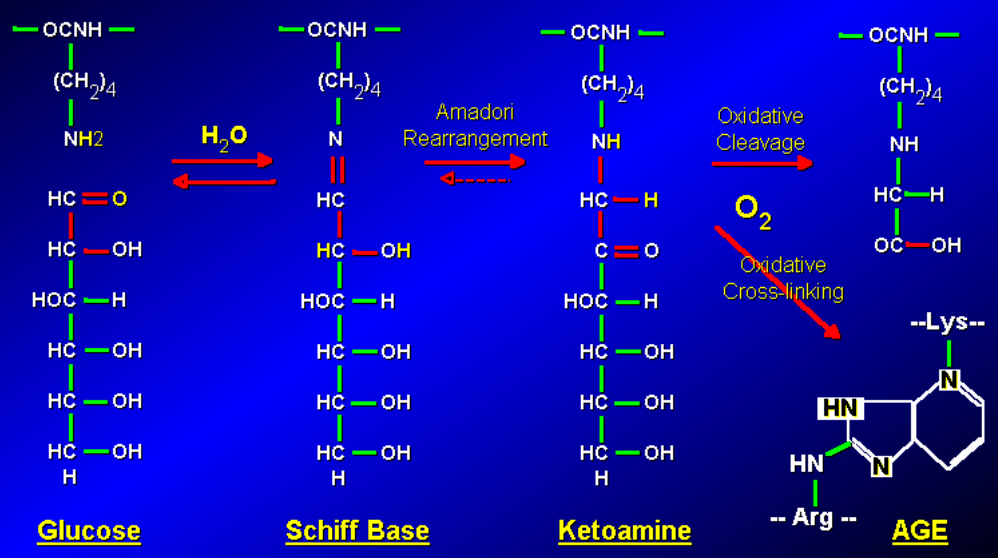
Diabetic Complications

Mechanisms:

- Elevated Fatty Acids (and abnormal lipoproteins)
- Altered cytokines, signaling molecules, and hormones
- Lipid accumulation: esp - muscle, liver, islets, heart
- Oxidative Stress: NADH/NAD$^+$, Super Oxide, Nitric Oxide
- Inflammation: NF-kB, Prostaglandins
- Hyperglycemia
  - Glycosylation – advanced glycosylation end products (AGE)
  - Inositol – Phosphoinositides → DAG, IP_3
  - Sorbitol – DAG → Protein Kinase C

Atherosclerosis: Advanced Glycosylation End Products

Lysine (or ARG) Residues in Proteins:



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Inositol → Phosphoinositides

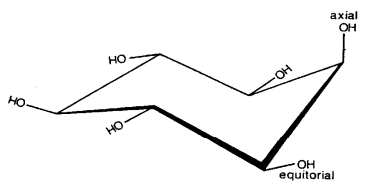
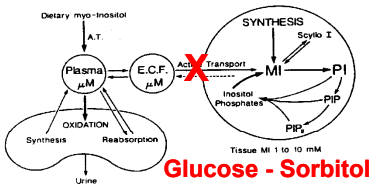


FIG. 3. *myo*-inositol, the principal inositol (cyclohexanehexols) in plasma and tissues, is characterized by single axial hydroxyl group at C-2; all of its other hydroxyl groups are equitorial. When equitorial hydroxyl group (*lower right*) is replaced by phosphoester bond in formation of phosphatidylinositol, the carbon involved in this bond is designated C-1.



Glucose - Sorbitol

FIG. 4. Outline of some aspects of *myo*-inositol metabolism. Phosphatidylinositol (PI), phosphatidylinositol 4-phosphate (PIP), and phosphatidylinositol 4,5-bisphosphate (PIP_2) are inositol-containing phospholipids that differ in number of phosphate groups attached to their *myo*-inositol moiety. *scyllo*-inositol (scyllo I) is a specific inositol.

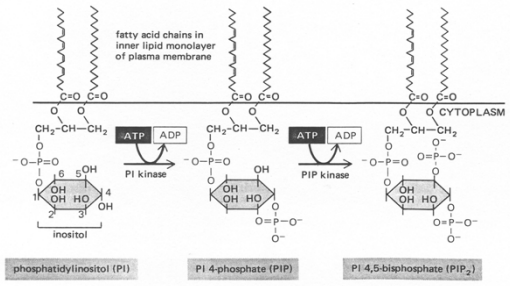
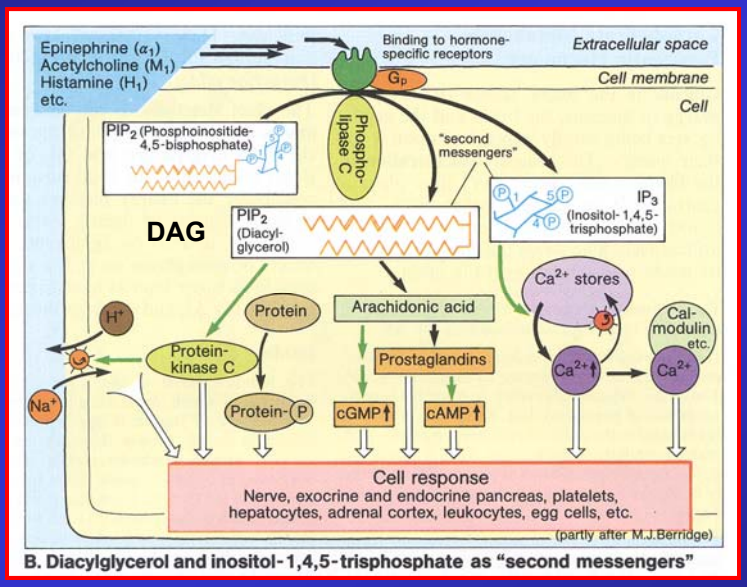


Figure 12–21 The inositol phospholipids (phosphoinositides) comprise less than 10% of the total phospholipids in mammalian cell membranes. The polyphosphoinositides (PIP and PIP_2) are produced by the phosphorylation of phosphatidylinositol (PI). Although all three inositol phospholipids may be broken down in the signaling response, it is the breakdown of PIP_2 that is most critical, even though it is the least abundant, constituting less than 10% of the total inositol lipids and less than 1% of the total phospholipids.

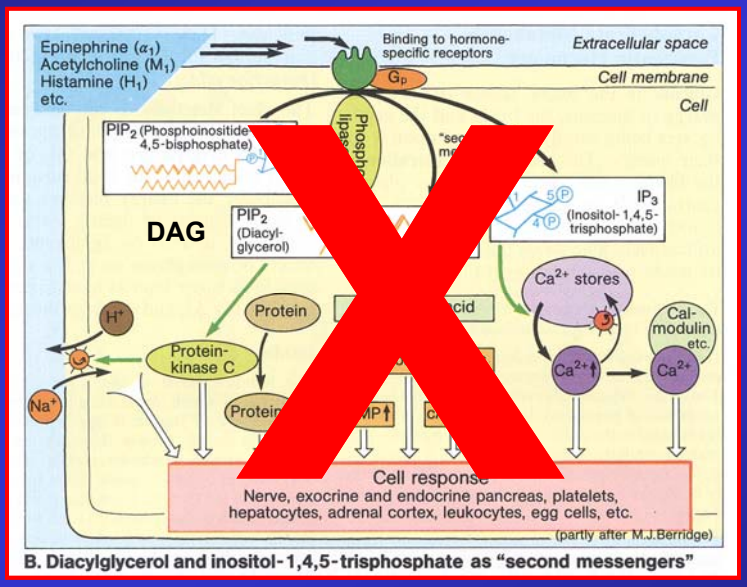
Inositol - Phosphoinositides



B. Diacylglycerol and inositol-1,4,5-trisphosphate as "second messengers"

Excess glucose blocks inositol uptake & phosphoinositide synthesis

Inositol - Phosphoinositides



B. Diacylglycerol and inositol-1,4,5-trisphosphate as "second messengers"

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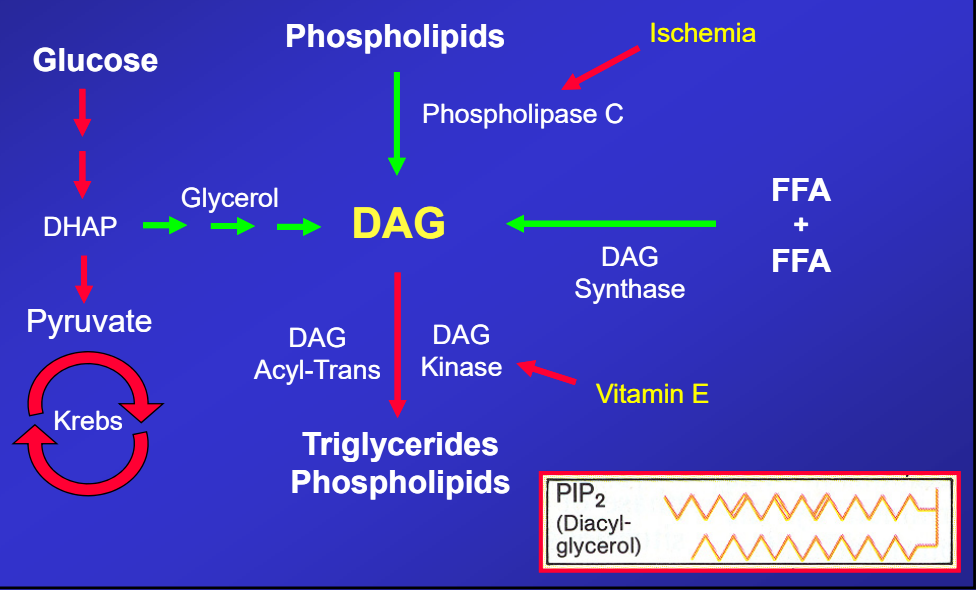
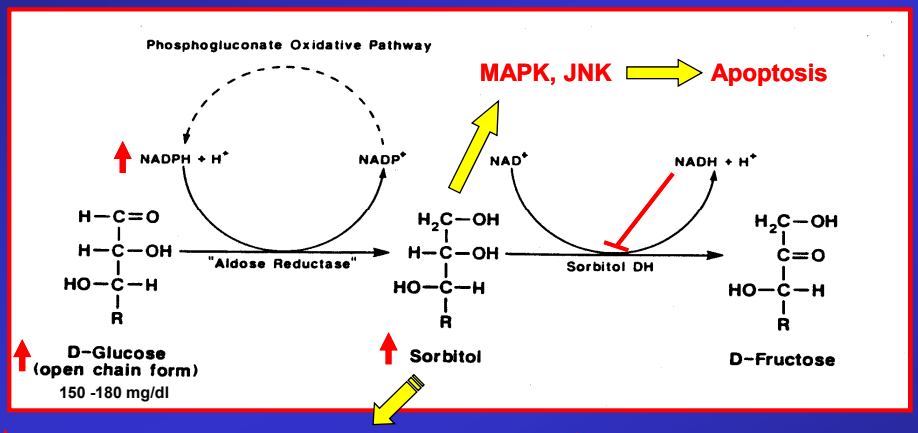
Glucose and Fatty Acids → Diacylglycerol (DAG)



Aldose Reductase - Sorbitol



↑ Osmolarity (AMPK), DAG synthase → ↑ DAG → ↑ PK-C

↑ ET-1, TGFb, PAI-1, VEGF, Super Oxide, Insulin Resistance & Cell Death

↓ Nitric Oxide

Atherosclerosis: Introduction

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Chemical - glycation, oxidation

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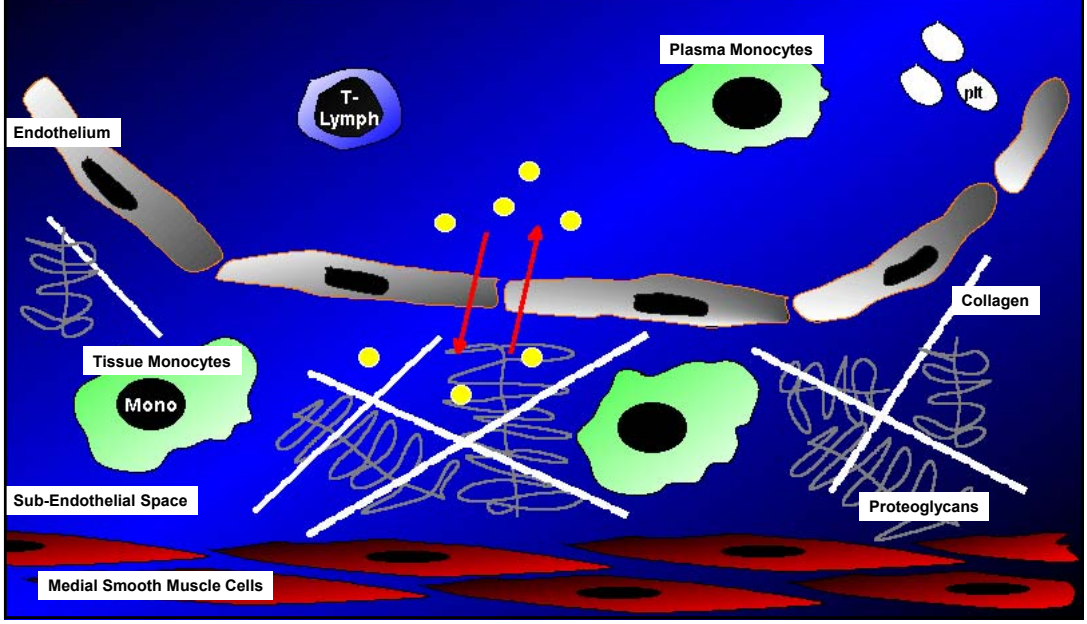
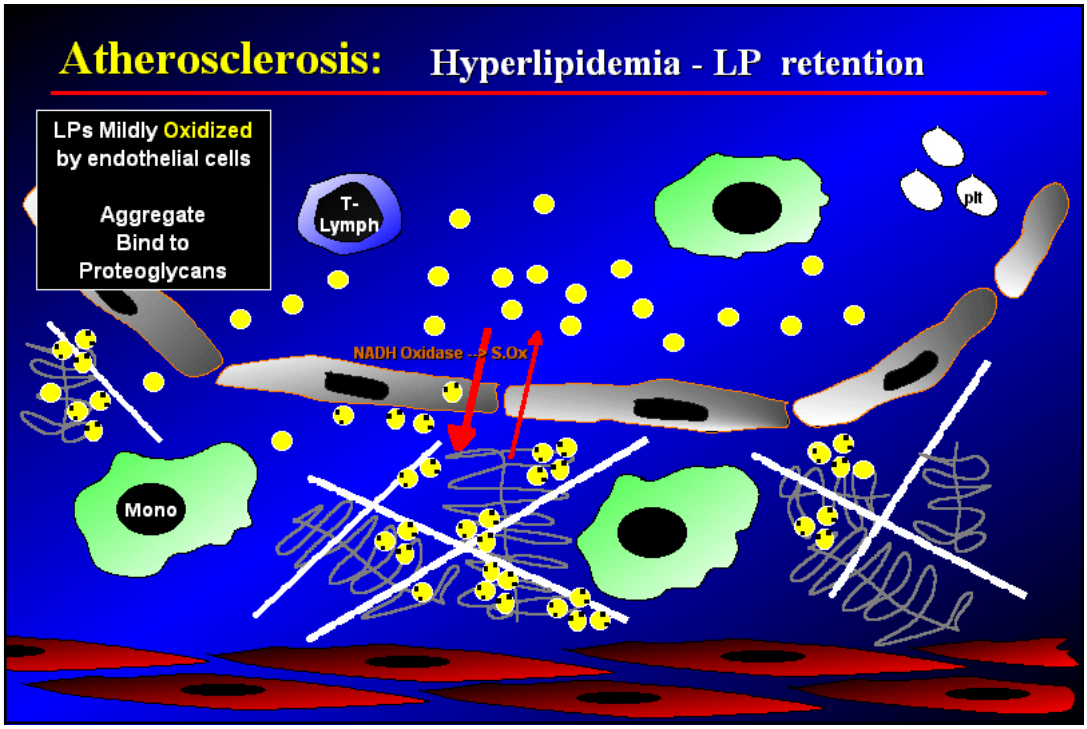
Vessal Wall - cells, matrix, and contraction

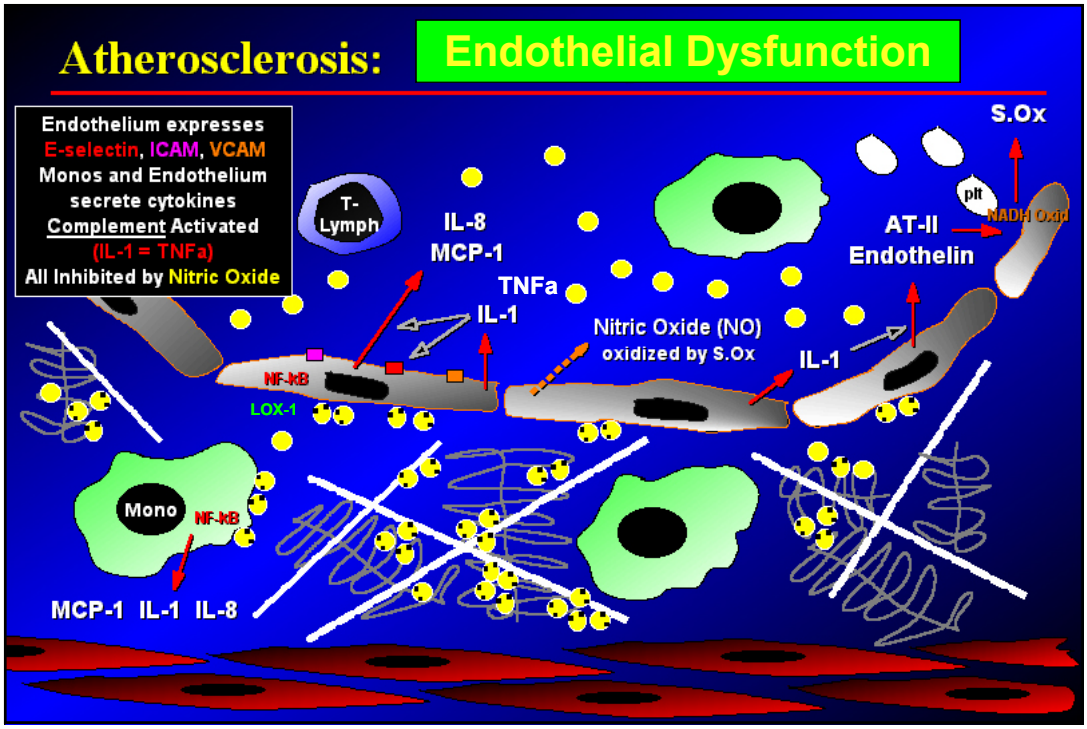
Coagulation - platelets, clottings factors, and fibrinolysis

Neovascularization

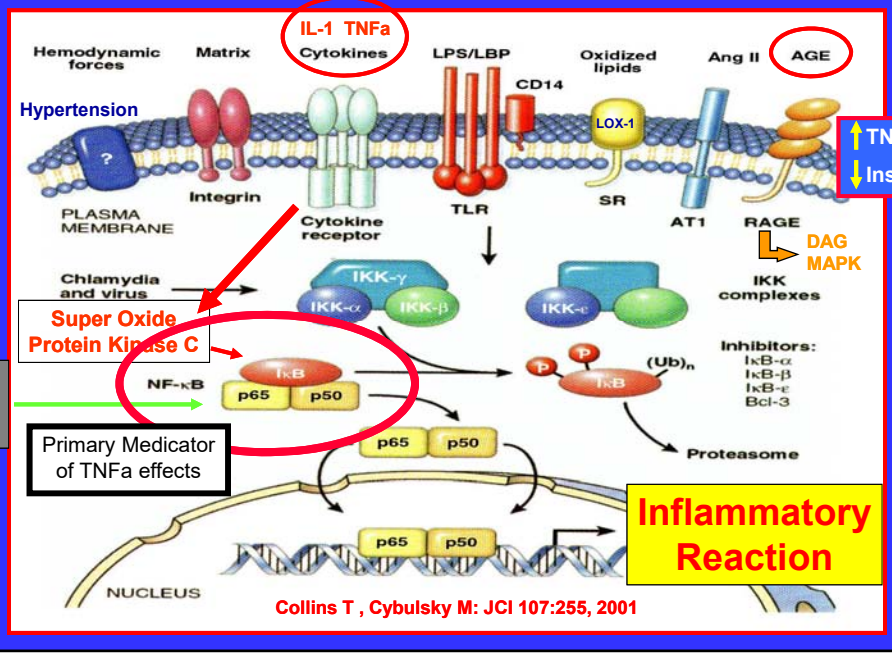
Atherosclerosis: Normal Vascular Metabolism




Atherosclerosis: Hyperlipidemia - LP retention
LPs Mildly Oxidized by endothelial cells
Aggregate
Bind to
Proteoglycans
T-Lymph
plt
NADH Oxidase --> S.Ox
Mono

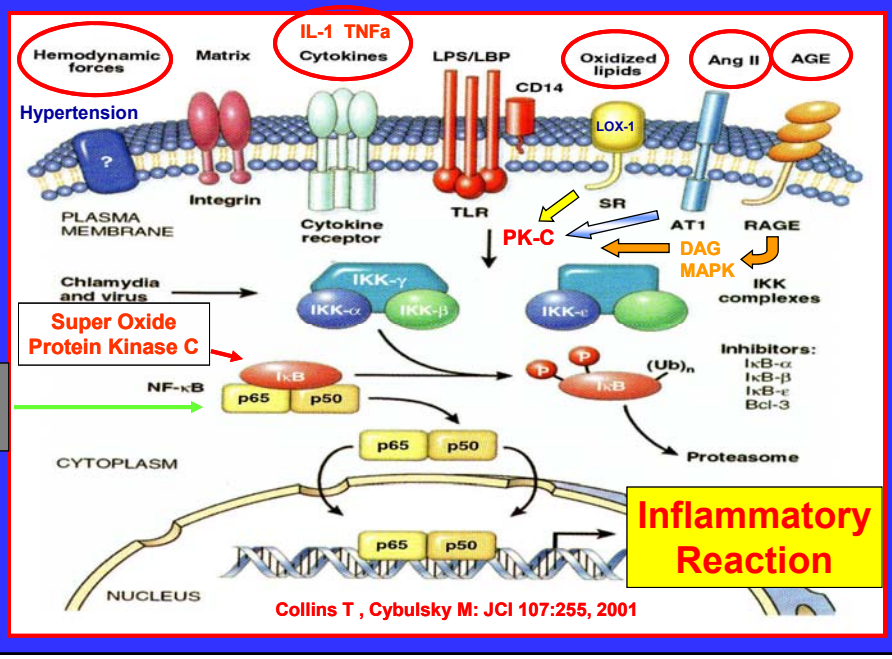

Atherosclerosis: Endothelial Dysfunction
Endothelium expresses
E-selectin, ICAM, VCAM
Monos and Endothelium
secrete cytokines
Complement Activated
(IL-1 = TNFa)
All Inhibited by Nitric Oxide
T-Lymph
IL-8
MCP-1
TNFa
IL-1
Nitric Oxide (NO)
oxidized by S.Ox
S.Ox
plt
NADH Oxid
AT-II
Endothelin
IL-1
NF-kB
LOX-1
Mono
NF-kB
MCP-1 IL-1 IL-8

Nuclear Factor kB (NF-kB) Activation



Collins T , Cybulsky M: JCI 107:255, 2001

Nuclear Factor kB (NF-kB) Activation



Collins T , Cybulsky M: JCI 107:255, 2001

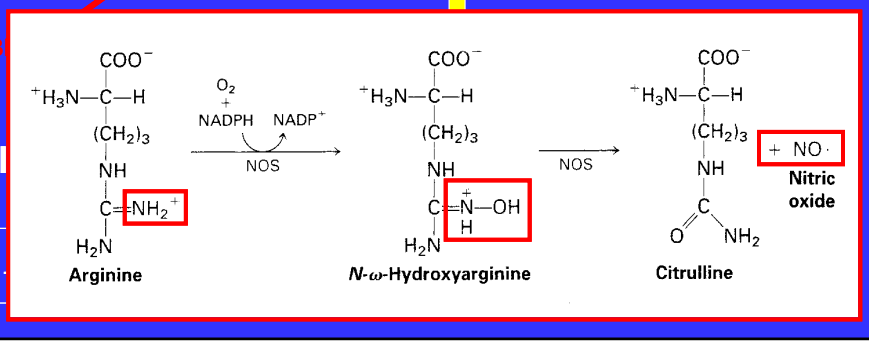
Nitric Oxide and Super Oxide

Nitric Oxide Synthase **(NOS)** activated by **bradykinin (ACEI, Amlo)**, acetylcholine, histamine, serotonin, thrombin, **estrogen,** substance P, shear stress, and **insulin**
Inhibited by asymmetric dimethylarginine **(ADMA - CRI)**

L-ARG —(**NOS**, **NADPH**)→ **L-Citrullin + NO** → **$ONOO^-$** **(peroxynitrite)**

NOS NADPH ↓ **L-Citrul**

BH4



SO converts

Nitric Oxide and Super Oxide

Nitric Oxide Synthase **(NOS)** activated by **bradykinin (ACEI, Amlo)**, acetylcholine, histamine, serotonin, thrombin, **estrogen,** substance P, shear stress, and **insulin**
Inhibited by asymmetric dimethylarginine **(ADMA - CRI)**

L-ARG —(**NOS**, **NADPH**)→ **L-Citrullin + NO** → **$ONOO^-$** **(peroxynitrite)**

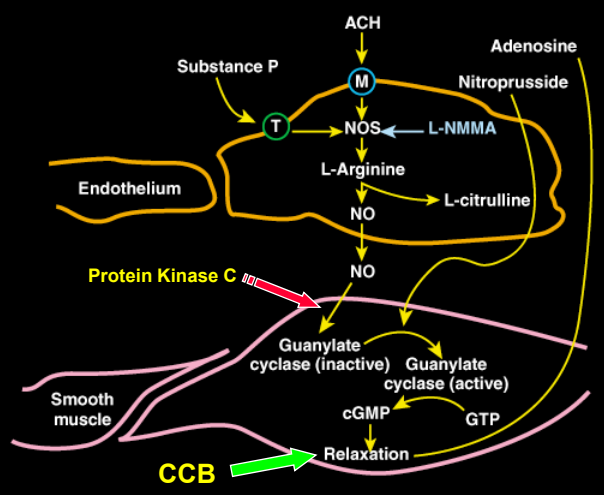
NOS NADPH ↓ **BH2** **L-Citrullin + SO**

BH4 ← **Super Oxide (SO = $O_2^{-\circ}$)** ← **NO**

BH4 is a required cofactor for NOS
SO converts Tetrahydrobiopterin **(BH4)** to Dihydrobiopterin **(BH2)** → BH4 deficiency

VBWG

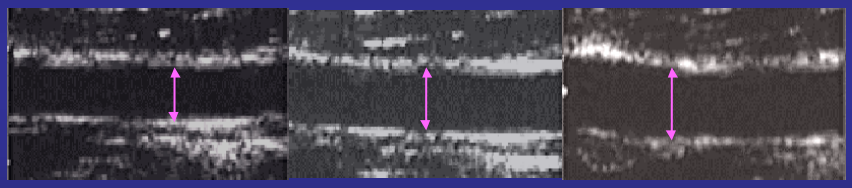
Physiology of NO in the human coronary and peripheral vasculature



Adapted from Quyyumi AA. *Am J Med.* 1998;105(1A):32S-39S.

Flow-Mediated Vasodilation (FMD) in the Brachial Artery

Baseline Diameter	Hyperemic Flow	Nitroglycerin

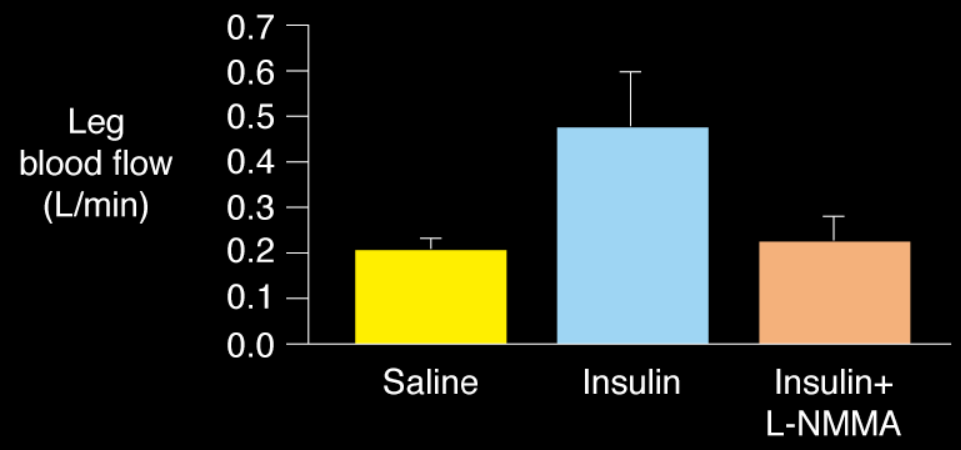


3.02 mm	3.34 mm	3.57 mm
Resting	10.6%	18.2%

Francois Charbonneau, 1996.

VBWG

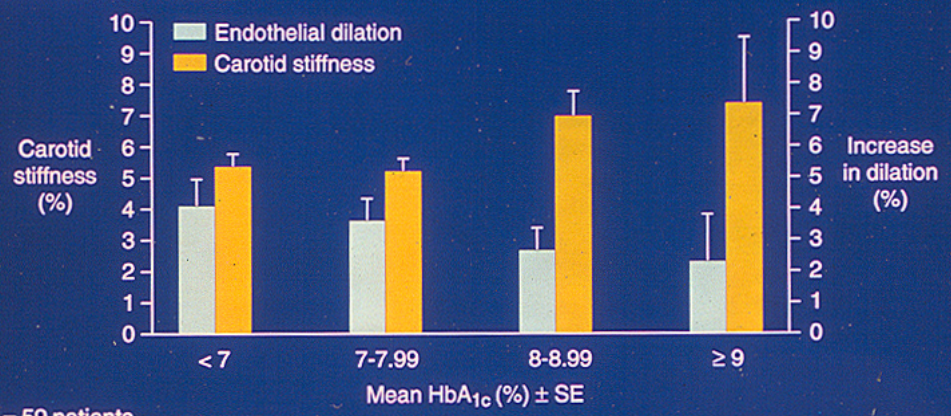
Insulin causes vasodilation via NO-dependent mechanism



Baron AD. *J Invest Med.* 1996;44:406-412.

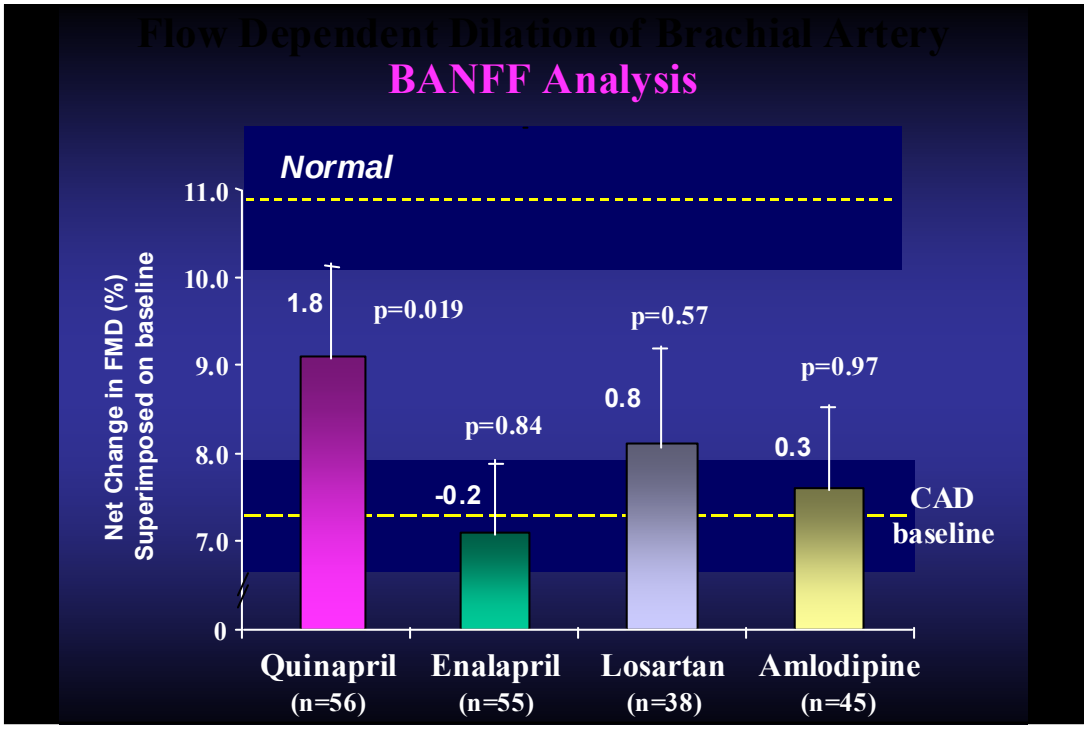
Stockholm Diabetes Intervention Study (SDIS)

Relationship of HbA_{1c} levels to endothelial dilation and carotid stiffness



N = 59 patients
Endothelium-dependent dilation as related to HbA_{1c}, $P = .028$
Wall stiffness correlated with HbA_{1c} during study, $P = .009$

Jensen-Urstad KJ, et al. Diabetes. 1996;45:1253-1258.



Diabetic Complications: Endothelial Dysfunction

Atorvastatin specifically improves endothelial dysfunction:

"In Vitro" Studies:

- ↓ oxLDL, NF-kB, NAD(P)H Oxidase, Endothelin
- ↑ Nitric Oxide

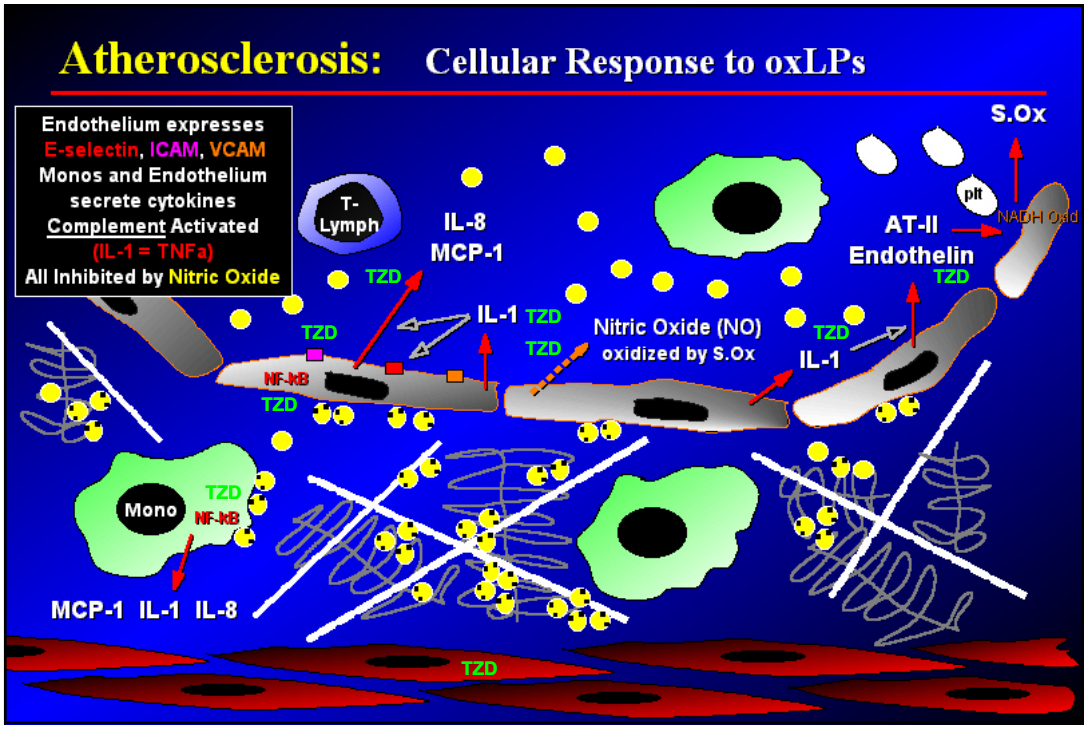
Animal Models

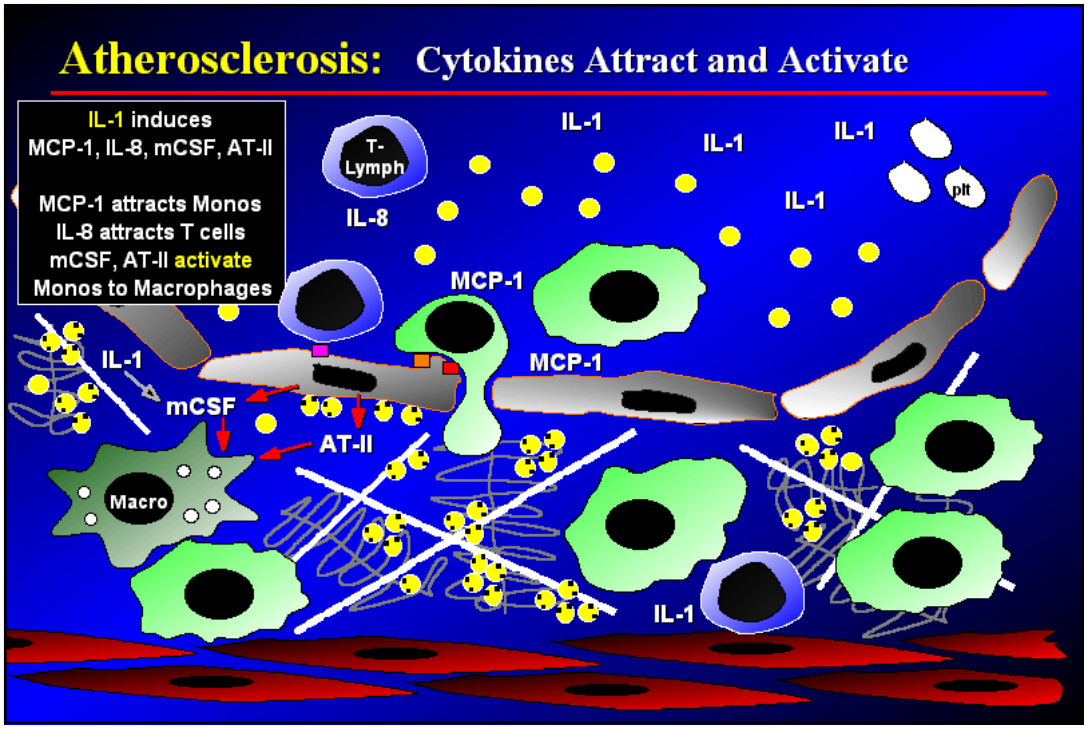
Hypertriglyceridemic Men (↓Factor VII)

Hypercholesterolemic Women and Men (2)

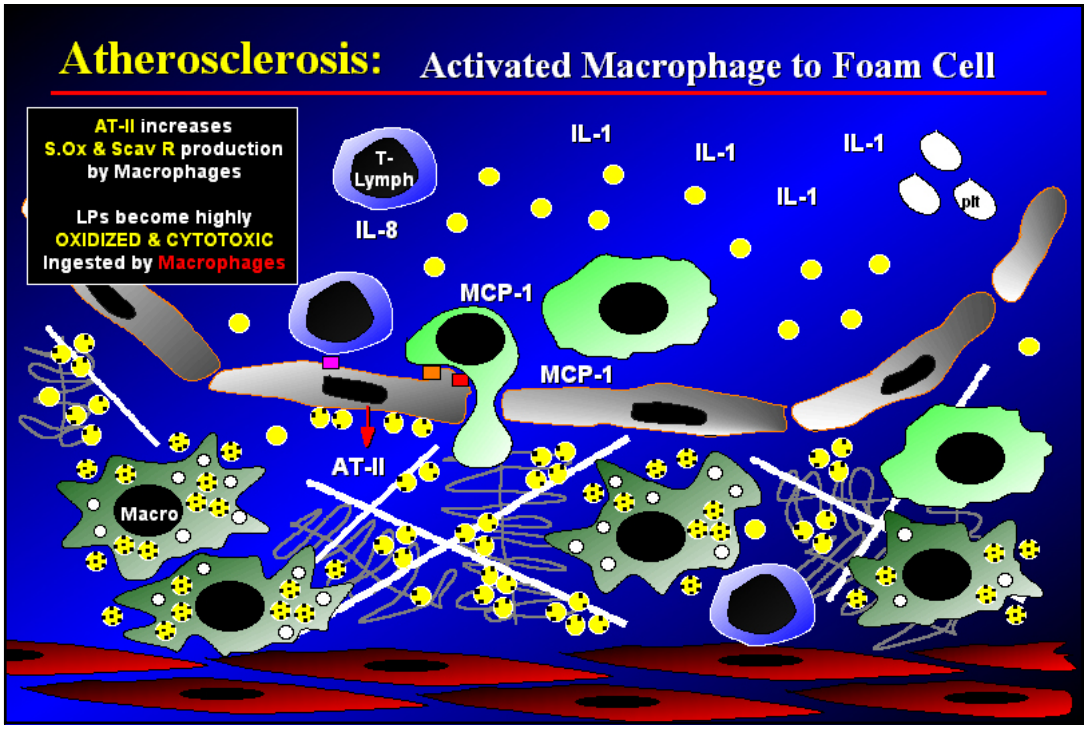
Severe Hypercholesterolemia and FH (2)

(Reduce microAlb and fibrinogen in Type 2 DM)


Atherosclerosis: Cellular Response to oxLPs
Endothelium expresses
E-selectin, ICAM, VCAM
Monos and Endothelium
secrete cytokines
Complement Activated
(IL-1 = TNFa)
All Inhibited by Nitric Oxide
T-Lymph
IL-8
MCP-1
TZD
IL-1
TZD
TZD
NF-kB
TZD
Nitric Oxide (NO)
oxidized by S.Ox
TZD
TZD
IL-1
S.Ox
plt
NADH Oxid
AT-II
Endothelin
TZD
Mono
TZD
NF-kB
MCP-1 IL-1 IL-8
TZD


Atherosclerosis: Cytokines Attract and Activate
IL-1 induces
MCP-1, IL-8, mCSF, AT-II
MCP-1 attracts Monos
IL-8 attracts T cells
mCSF, AT-II activate
Monos to Macrophages
T-Lymph
IL-8
IL-1
IL-1
IL-1
IL-1
plt
MCP-1
MCP-1
IL-1
mCSF
AT-II
Macro
IL-1

Atherosclerosis: Activated Macrophage to Foam Cell



Matrix Production

Collagen: (Fibrosis)
Matrix Framework
Stimulated by TGF-b (PK-C)
Inhibited by NO
(via cGMP - blocked by PK-C)

Proteoglycans (PGC):
Filler Material (Leakage)
Selectivity → Charge & Size

Hyperglycemia:
Synthesis: (Amlo ---| pro-coll)
↑ Collagen via TGF-b
↓ PGC via PK-C
Crosslinks: Collagen →
↑ Rigidity ↓ Degradation
↓ Binding of PGC

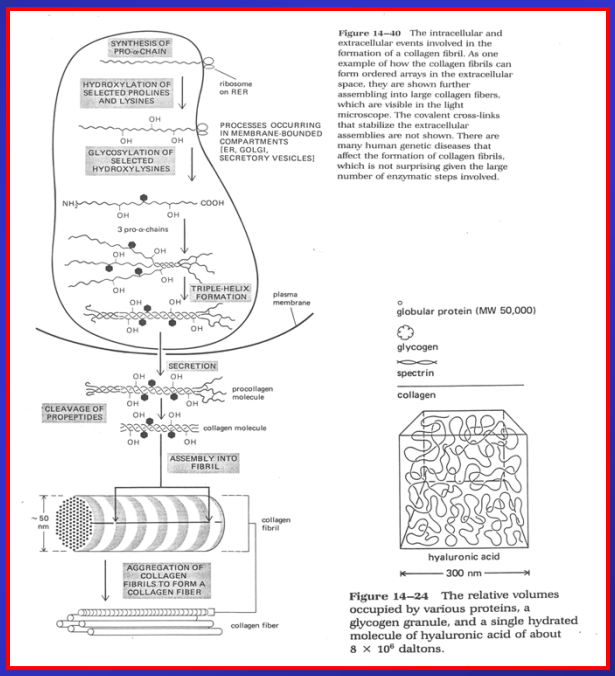
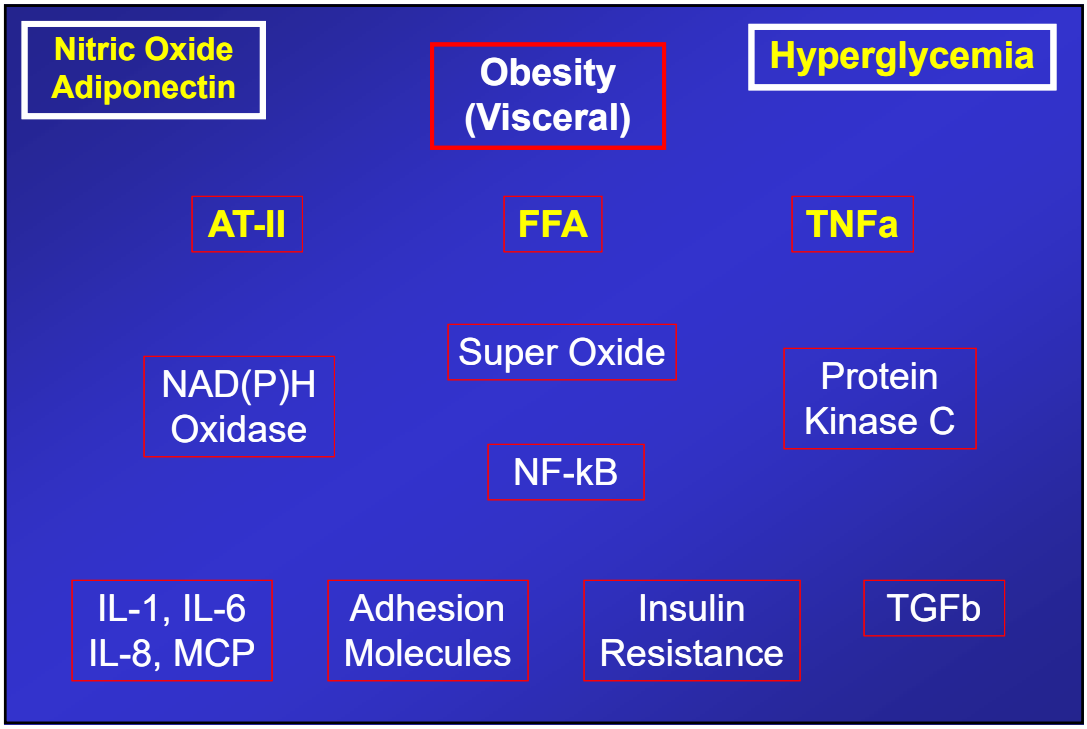
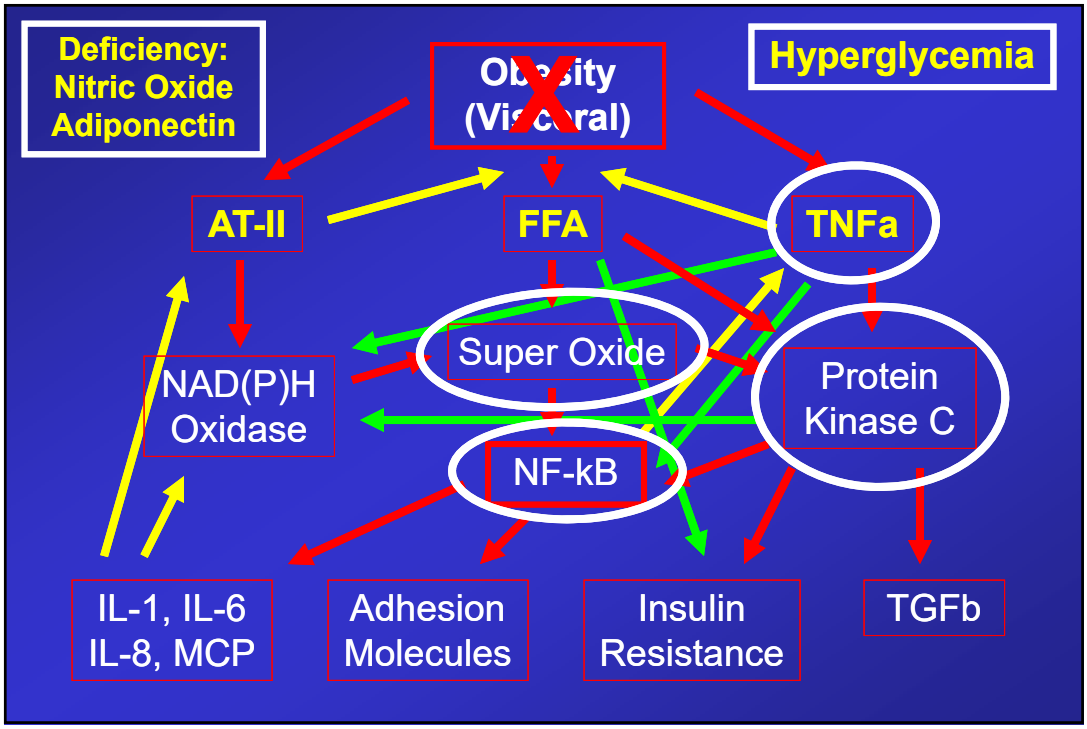


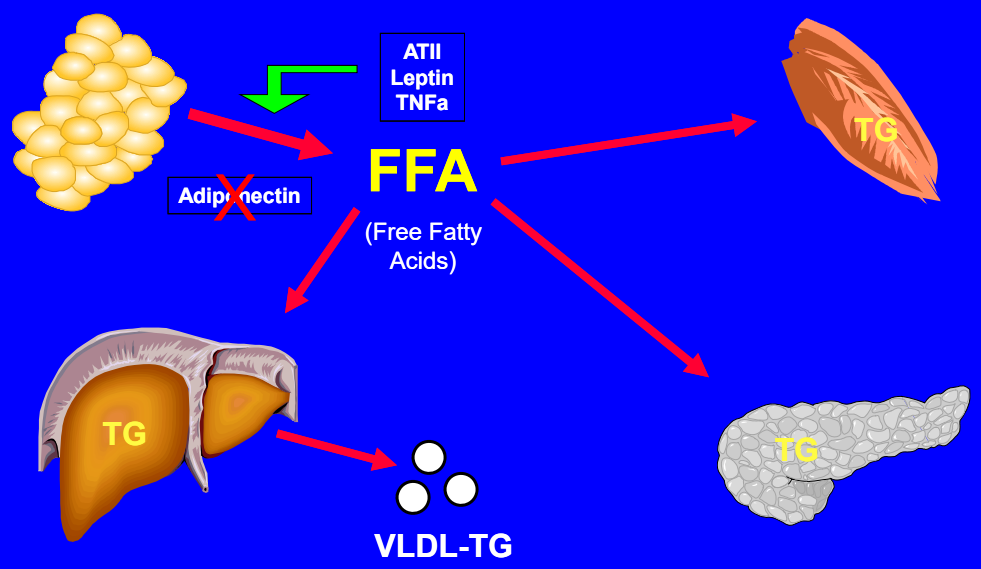
Figure 14–40 The intracellular and extracellular events involved in the formation of a collagen fibril. As one example of how the collagen fibrils can form ordered arrays in the extracellular space, they are shown further assembling into large collagen fibers, which are visible in the light microscope. The covalent cross-links that stabilize the extracellular assemblies are not shown. There are many human genetic diseases that affect the formation of collagen fibrils, which is not surprising given the large number of enzymatic steps involved.

Figure 14–24 The relative volumes occupied by various proteins, a glycogen granule, and a single hydrated molecule of hyaluronic acid of about 8×10^6 daltons.

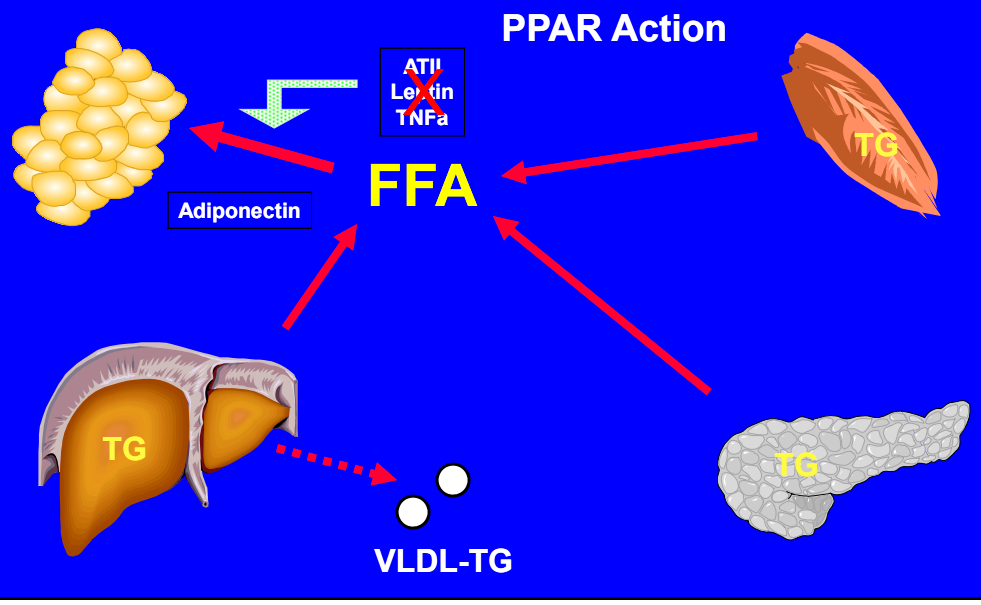

Nitric Oxide
Adiponectin
Obesity
(Visceral)
Hyperglycemia
AT-II
FFA
TNFa
Super Oxide
NAD(P)H
Oxidase
Protein
Kinase C
NF-kB
IL-1, IL-6
IL-8, MCP
Adhesion
Molecules
Insulin
Resistance
TGFb


Deficiency:
Nitric Oxide
Adiponectin
Obesity
(Visceral)
Hyperglycemia
AT-II
FFA
TNFa
Super Oxide
NAD(P)H
Oxidase
Protein
Kinase C
NF-kB
IL-1, IL-6
IL-8, MCP
Adhesion
Molecules
Insulin
Resistance
TGFb

Insulin Resistance Syndrome



PPAR: Peroxisome Proliferator-Activated Receptor



Atherosclerosis: Introduction

Impact of Diabetes (Types I & II) on Atherogenesis:

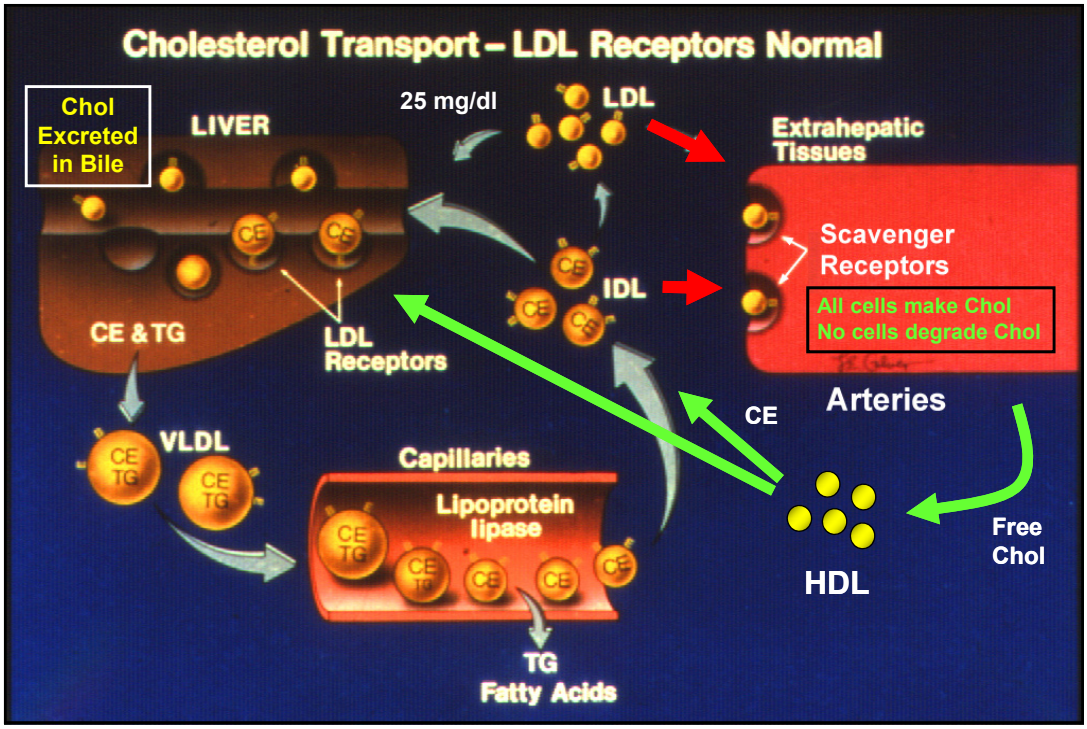
Metabolic - hyperglycemia, hyperinsulinemia
Chemical - glycation, oxidation

Lipoproteins, Apolipoproteins, and Lipids

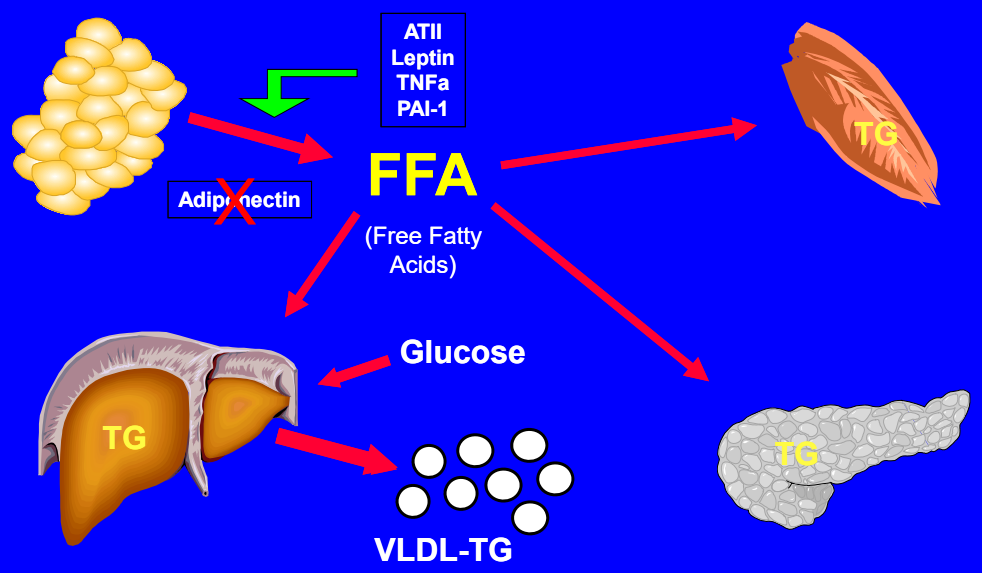
Vessal Wall - cells, matrix, and contraction

Coagulation - platelets, clottings factors, and fibrinolysis

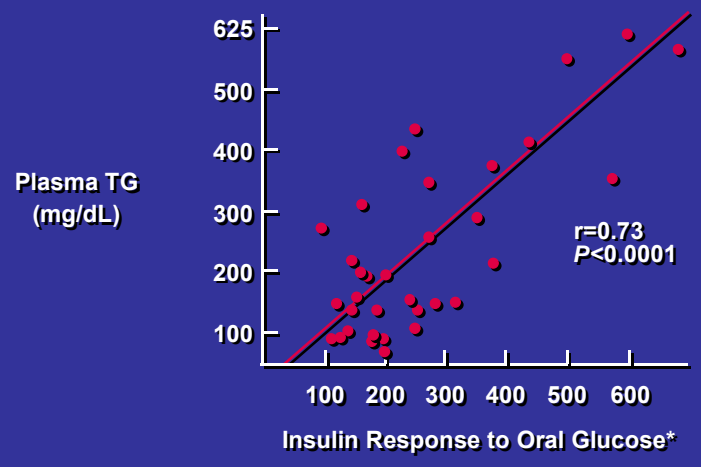
Neovascularization



Insulin Resistance Syndrome



Relation Between Insulin Resistance and Hypertriglyceridemia



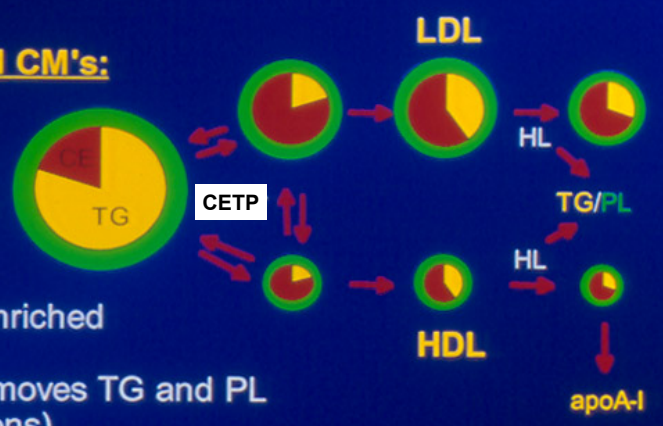
*Total area under 3-hour response curve (mean of 2 tests).

Olefsky JM, et al. *Am J Med*. 1974;57:551-560.

Atherosclerosis: Effects of Hypertriglyceridemia

Excess VLDL, IDL, and CM's:

Exchange TG and CE: "Chol. Ester Transfer Protein" (CETP)



LDL and HDL ---> TG-enriched

Hepatic Lipase (HL) removes TG and PL
(↑insulin and androgens)

HDL and LDL become small and more dense

ApoA-I is shed from smaller HDL particles --> ↑catabolism

Atherosclerosis: Small, Dense LDL

Atherogenicity of Small, Dense LDL:

Reduced binding to LDL receptor ---> prolonged plasma circulation

More easily glycated and oxidized ---> removed by scav. receptor

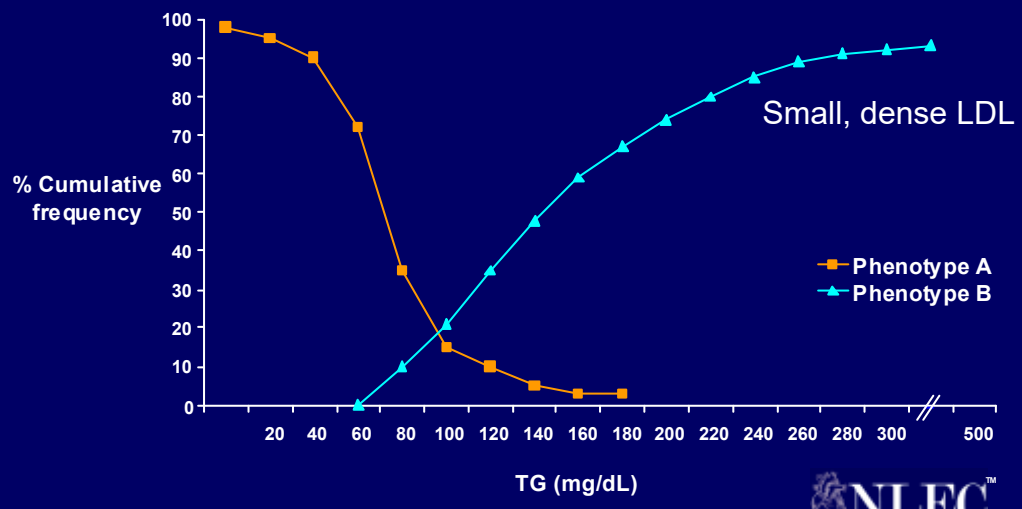
LDL catabolism diverted from Liver ---> Arterial Plaques

Better substrate for Hepatic Lipase ---> further size reduction

Easier transit through endothelial layer

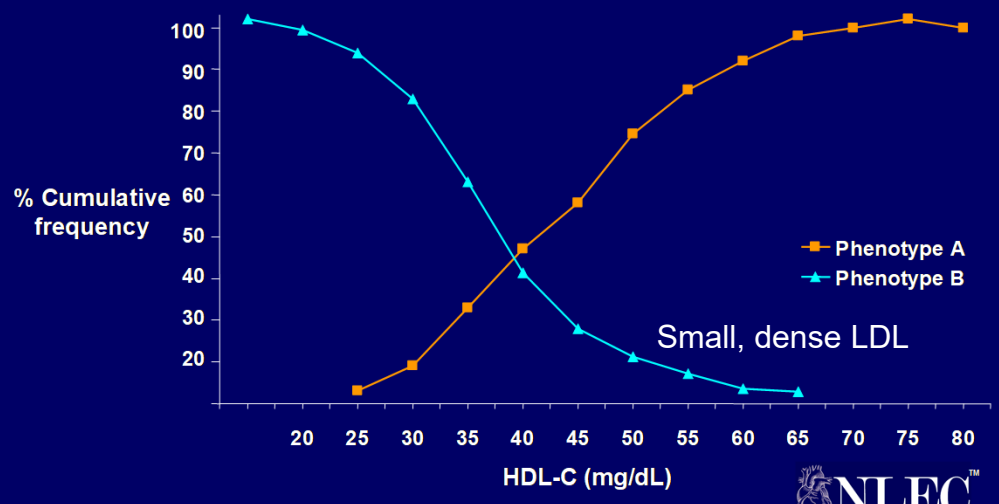
Increased binding to collagen in subendothelial space

Cumulative Distribution of Adjusted Plasma TG Levels: LDL Phenotypes A and B



Austin M et al. *Circulation*. 1990;82:495-506.

Cumulative Distribution of Adjusted HDL-C: LDL Phenotypes A and B



Austin M et al. *Circulation*. 1990;82:495-506.

Alterations of Lipoproteins in Diabetes

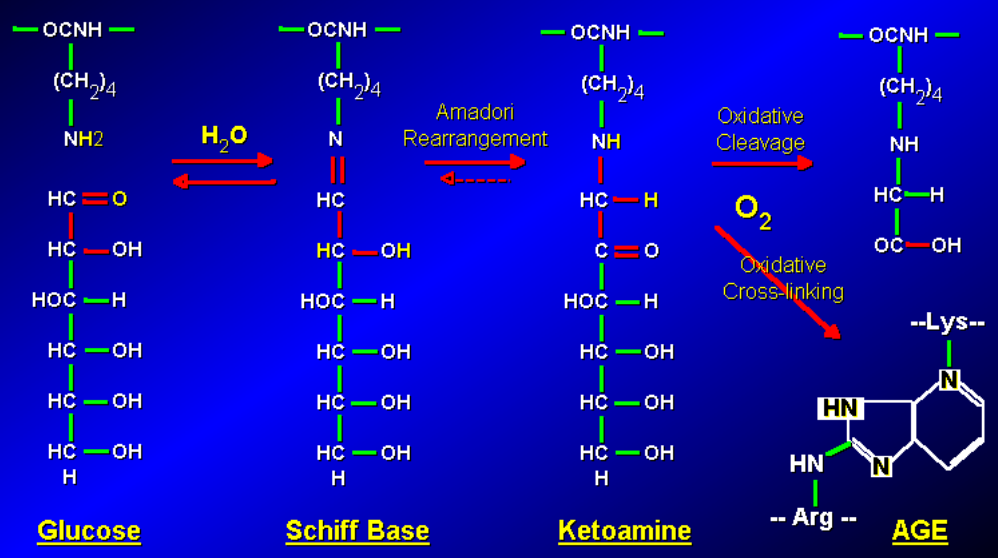
Concentration

- Hypertriglyceridemia due to increased VLDL levels
- Increased levels of remnants of triglyceride-rich lipoproteins
- Low levels of HDL (normal in treated IDDM)
- Decreased HDL_{2b}
- LDL levels +/- normal (improve with glycemic control)
- ? increased levels of Lp(a)
- Hyper-apoB

Chait A, Bierman EL. *Joslin's Diabetes Mellitus*. 1994;648–664.

Atherosclerosis: Advanced Glycosylation End Products

Lysine (or ARG) Residues in Proteins:

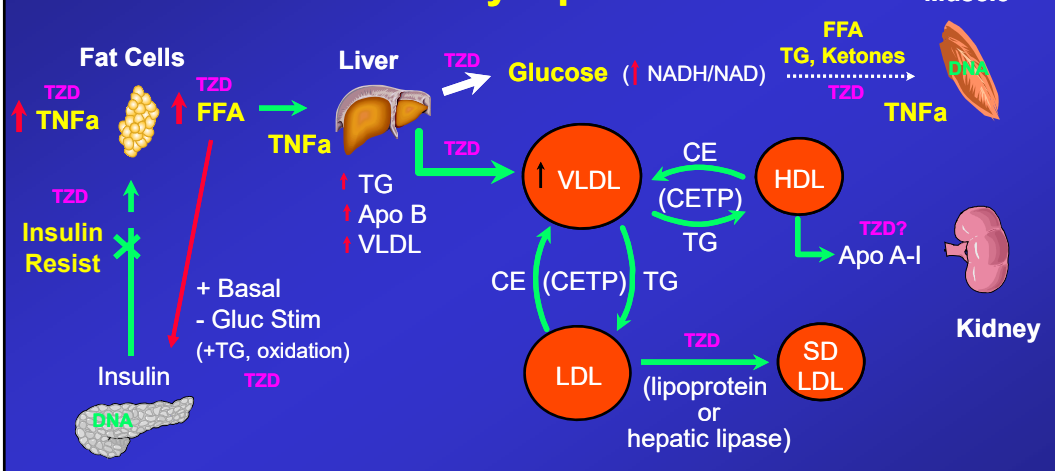


Atherosclerosis: Glycoxidation Effects on Lipoproteins

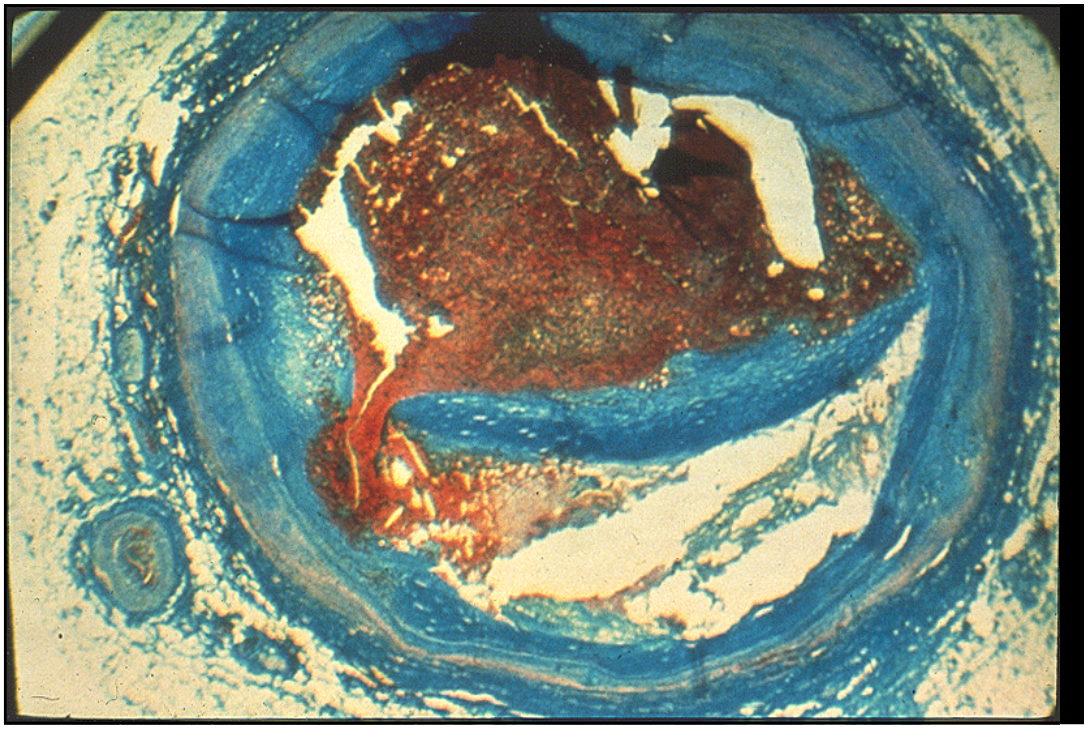
- ↓ Binding of VLDL, LDL to normal receptors ---> slow clearance from plasma
- ↑ Binding to scavenger and AGE receptors ---> divert lipoproteins to non-physiologic cells
- ↑ Binding to collagen ---> accumulation in vessal wall
- ↓ Efflux of chol. from cells into HDL; ↓ Blockade of mono adhesion
- ↑ HDL clearance ---> ↑ HL activity
- ↑ Immunogenicity ---> antibody-antigen complexes

Make lipoprotein-lipid cytotoxic to ET, SMC, and Macrophages

Mechanisms Relating Insulin Resistance and Dyslipidemia



Contributing Factors: Genetics, Visceral Obesity, Hypercortisolism, Hyperandrogenism



Atherosclerosis: Introduction

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- Metabolic - hyperglycemia, hyperinsulinemia
- Chemical - glycation, oxidation

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- Vessal Wall - cells, matrix, and contraction
- Coagulation - platelets, clottings factors, and fibrinolysis
- Neovascularization

Atherosclerosis: Coagulation Response to IL-1

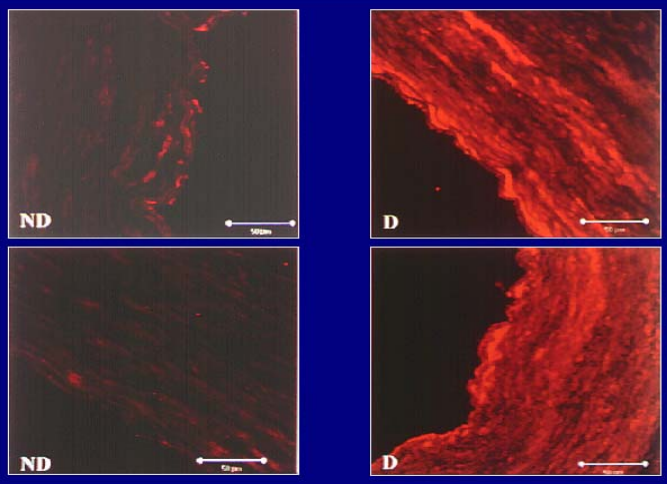
IL-1 induces Tissue Factor which activates VII & XII

CVD: Factors in yellow

DM: Fibrinogen, PAI-1, plt-aggreg elevated

Protein C+S
VIIIa XIa
X
AT III
Prothrombin
IL-1
XIa
C+S
Xa Va
Fibrinogen
XIIa
XI
Thrombin
XII
X
BK
VIIa
VII
Nitric Oxide
plt
Lp(a)
t-PA
PAI-1
AT-II
AGE
TNFa
Ins
Plasmin
Plasminogen
XL-Fibrin
Macro

PAI-1 in Internal Mammary Arteries of People With and Without Diabetes



ND = no diabetes; D = diabetes.

Pandolfi A et al. *Arterioscler Thromb Vasc Biol.* 2001;21:1378-1382.

Atherosclerosis: Introduction

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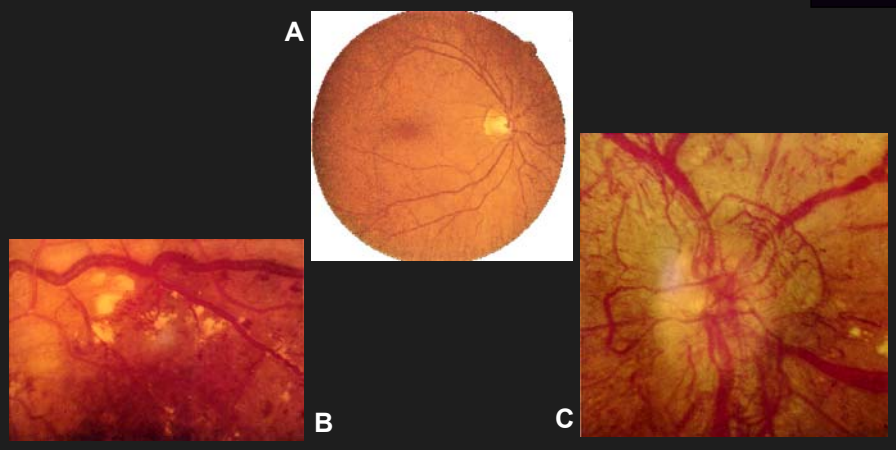
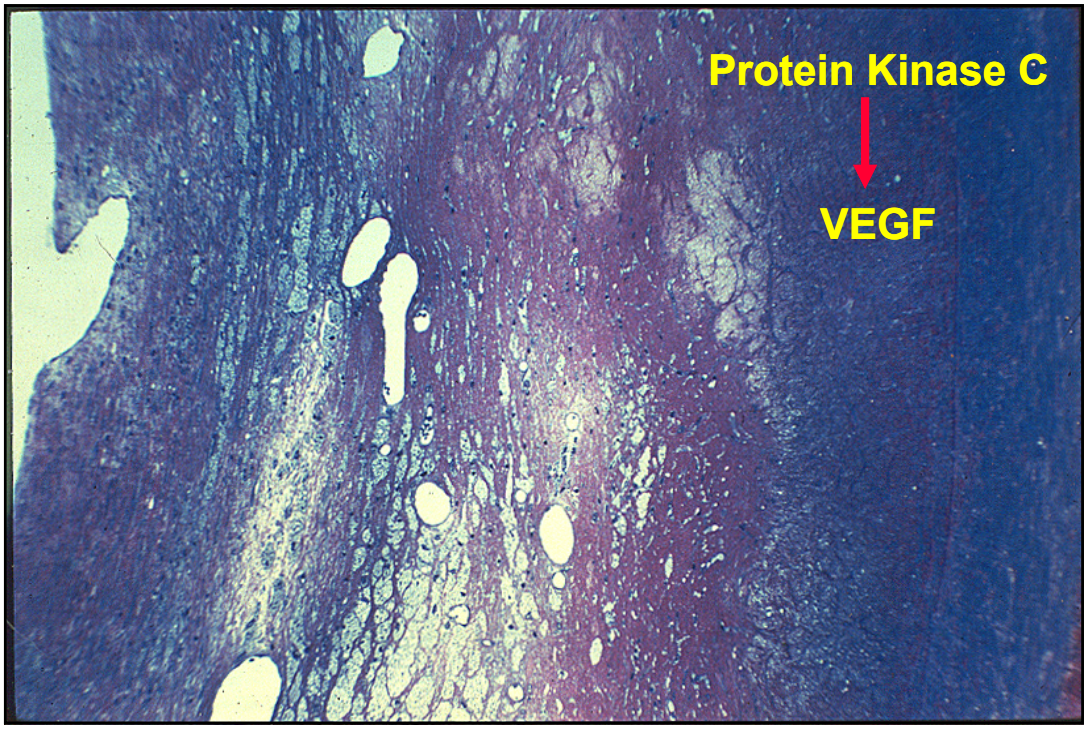
Neovascularization

Diabetic Retinopathy



Hall R, et al. Diabetes mellitus. In: *A Colour Atlas of Endocrinology*. 2nd ed. 1990:chap 7.


Protein Kinase C
VEGF

Diabetic Complications

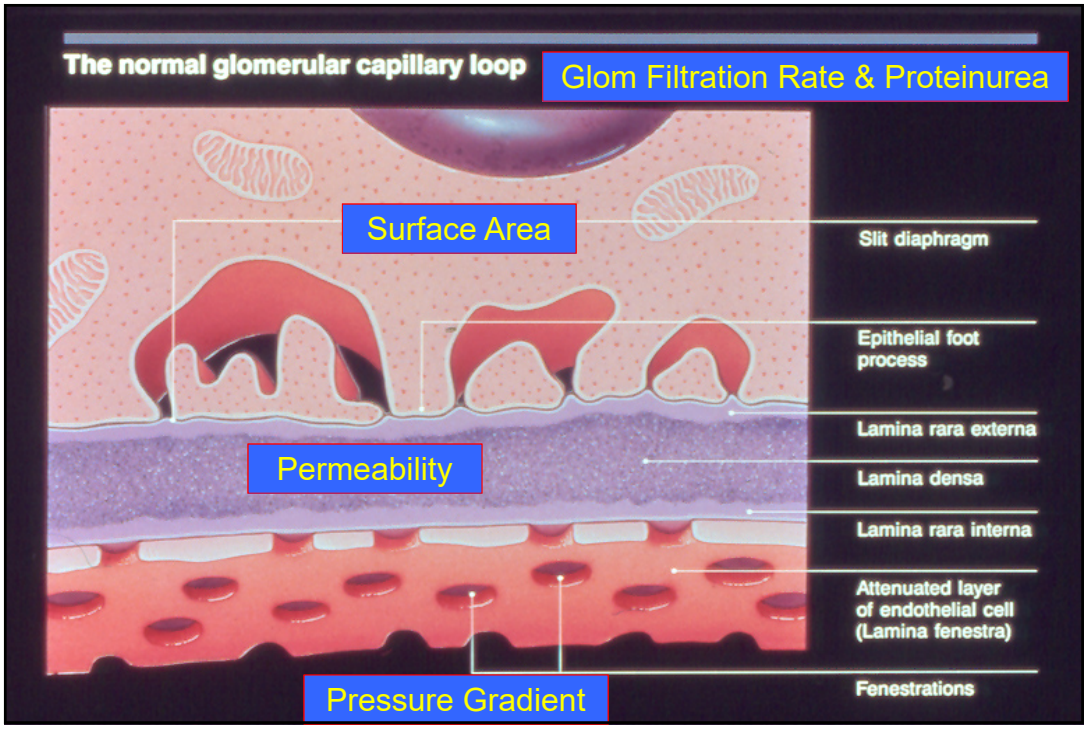
Chronic

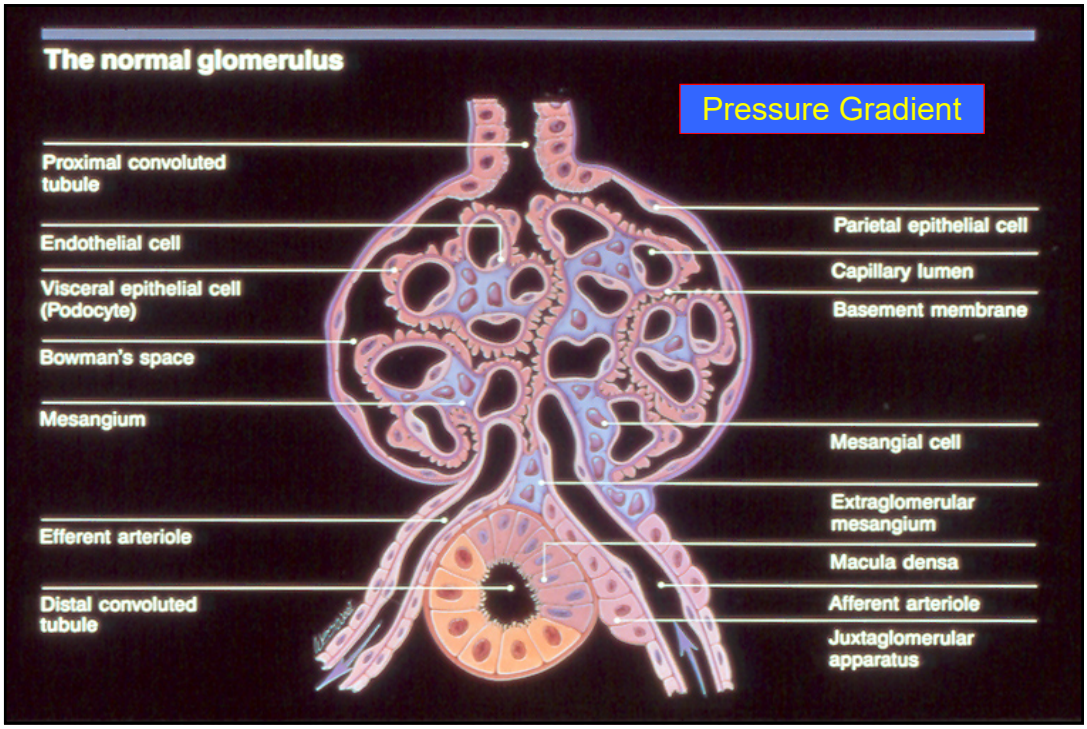
Triopathy:

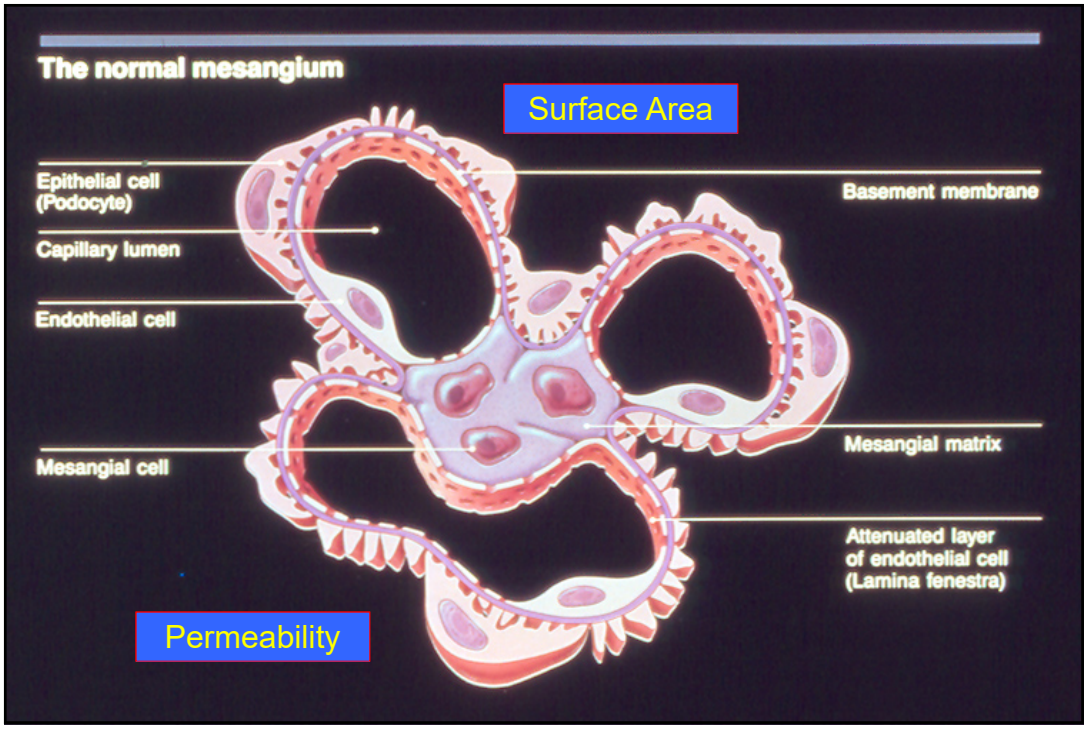
Nephropathy

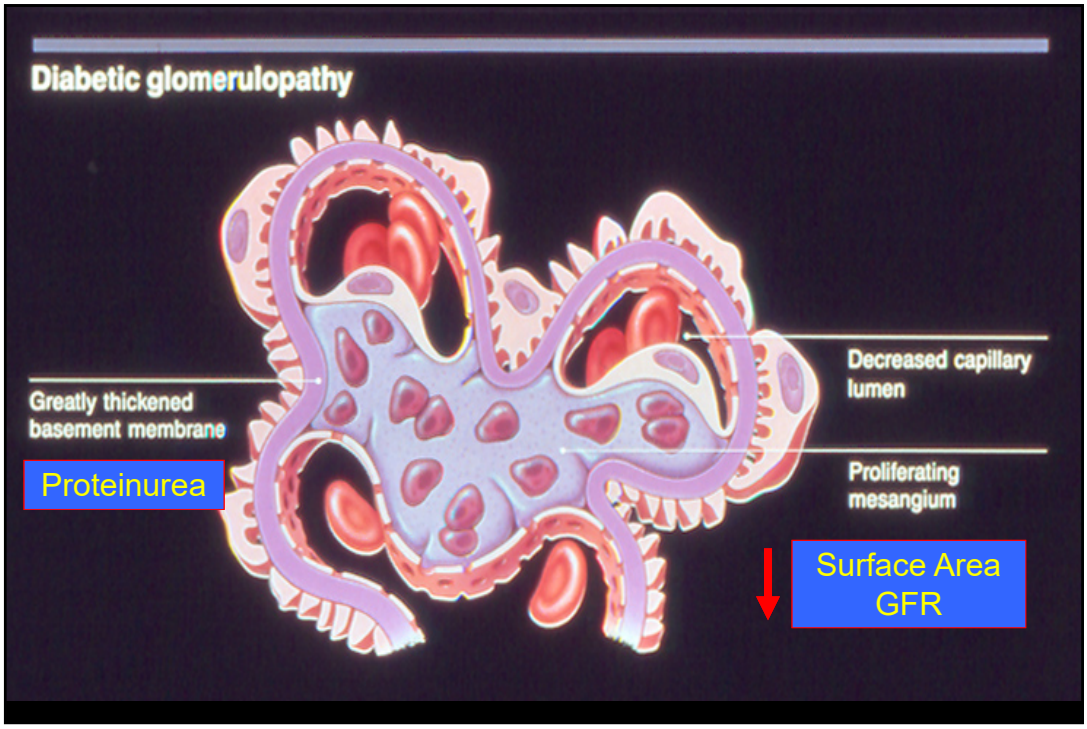
Retinopathy

Neuropathy

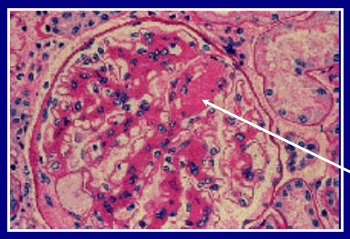



The normal glomerulus
Pressure Gradient
Proximal convoluted tubule
Endothelial cell
Visceral epithelial cell (Podocyte)
Bowman's space
Mesangium
Efferent arteriole
Distal convoluted tubule
Parietal epithelial cell
Capillary lumen
Basement membrane
Mesangial cell
Extraglomerular mesangium
Macula densa
Afferent arteriole
Juxtaglomerular apparatus


The normal mesangium
Surface Area
Epithelial cell (Podocyte)
Capillary lumen
Endothelial cell
Mesangial cell
Basement membrane
Mesangial matrix
Attenuated layer of endothelial cell (Lamina fenestra)
Permeability



Glomerular Pathology: Type 1 vs Type 2 Diabetes

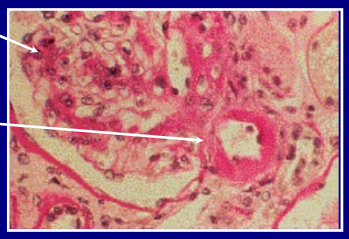


Type 1

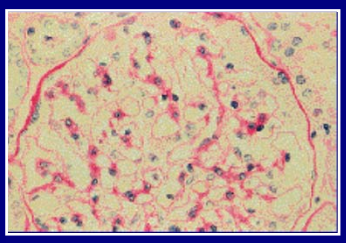
Accumulation of mesangial matrix material

Arteriosclerotic vessel

Accumulation of mesangial matrix material



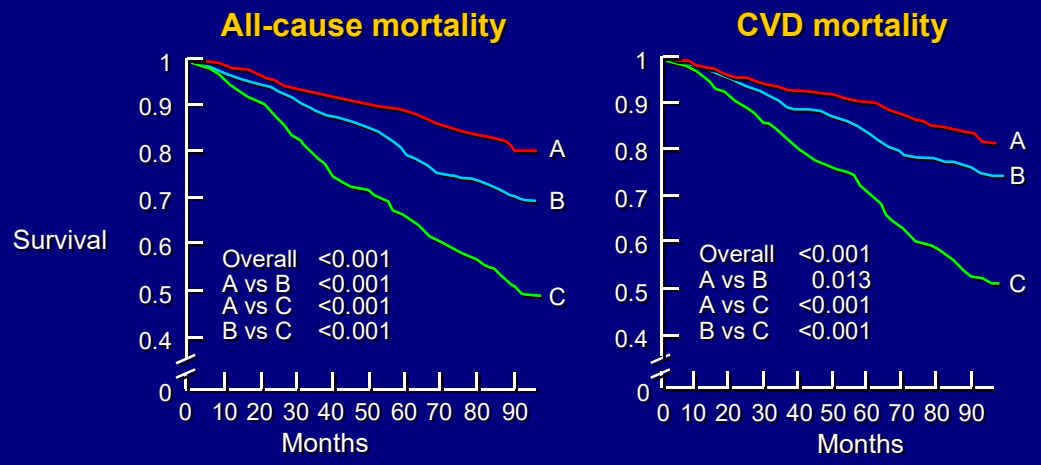
Type 2



Normal

Courtesy of Michael Steffes, MD.

Effect of Proteinuria on All-Cause and CVD Mortality in Patients With Type 2 Diabetes

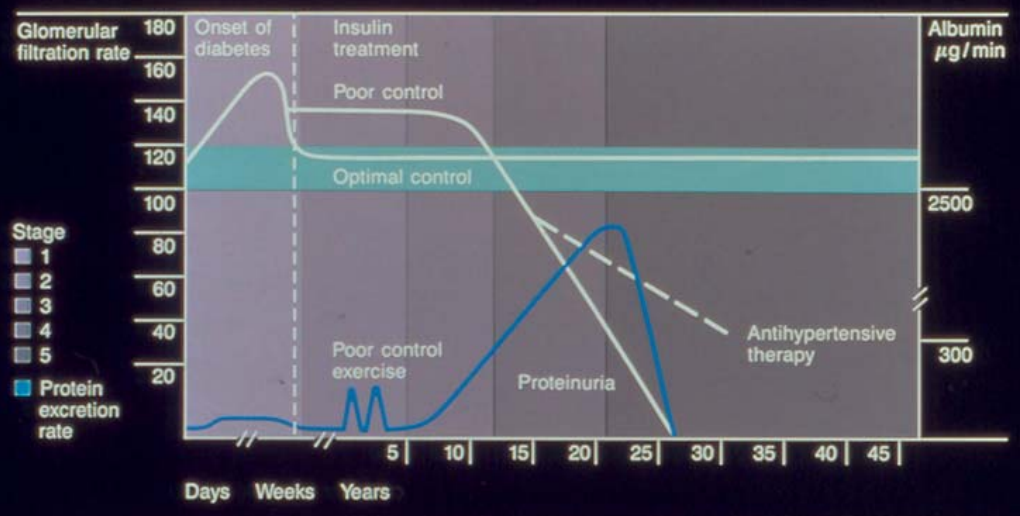


Urinary protein A: <150 mg/L B: 150-300 mg/L C: >300 mg/L

II.17 ©1998 PPS

Miettinen H et al. *Stroke*. 1996;27:2033-2039.

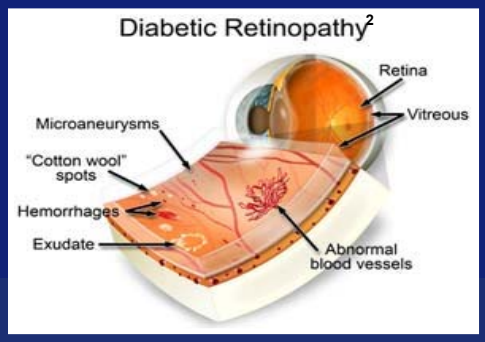
The stages of diabetic nephropathy



Adapted with permission from the American Diabetes Association, Inc., from Mogensen CE, Vittingus E: The stages in diabetic renal disease. *Diabetes* 1983; 32 (suppl 2); 64-68 and also with permission from Hostetter TH: Diabetic nephropathy, in Brenner BM, Rector FC Jr (eds): The Kidney. 3d ed., Philadelphia, PA: WB Saunders Co; 1986: chap 31.

Diabetic Retinopathy: Number One Cause Of Vision Loss In Working-age Americans[1]

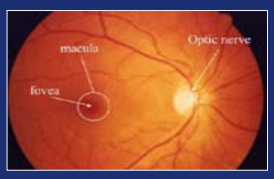
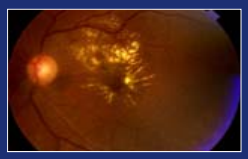
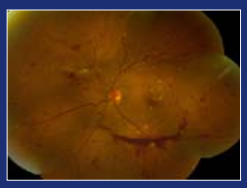
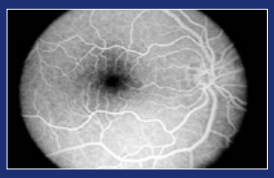
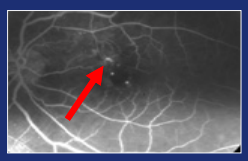
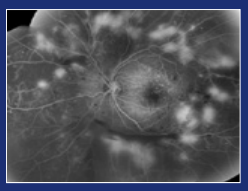
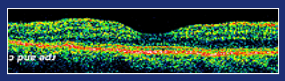
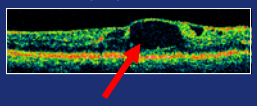
- Common microvascular complication of diabetes[1]
- Pathologic changes to blood vessels of the retina, leading to ischemia, neovascularization, and/or leakage (macular edema)[1]



1. The American Academy of Ophthalmology Retina Panel. Preferred Practice Pattern®: Diabetic retinopathy. Available at www.aao.org/education/library/ppp/upload/Diabetic-Retinopathy.pdf. Accessed: September, 2006.
2. EyeMDLink.com.Available at: http://wwwedymdlink.com/Condition.asap?ConditionID=3. Accessed: September, 2006.

ACCELMED®

Images of Diabetic Retinopathy

	Normal	Nonproliferative	Proliferative
Fundus Photograph			
Fundus Photograph			
Fluorescein Angiography Dys pigment epith (removal) Leaky capillaries	 15 seconds	 Capillary hypo-perfusion	
Optical Coherence Tomography			

Images: Courtesy of Mark Blumenkranz, MD

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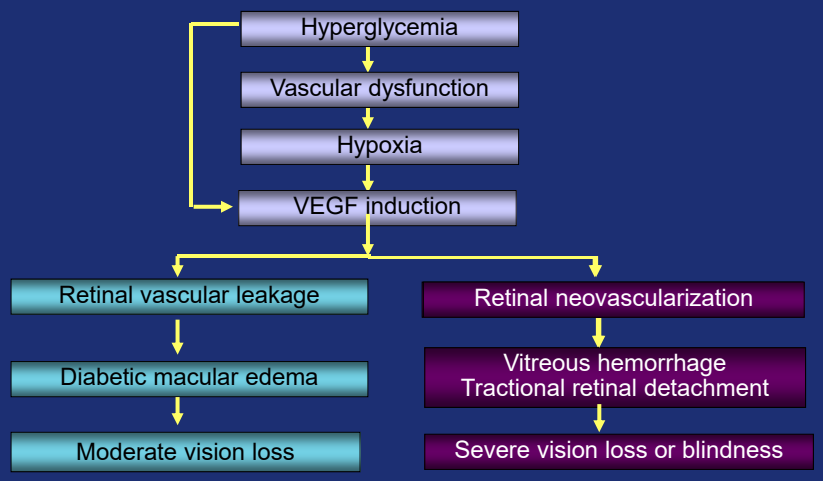
Potential Pathways for Vision Loss in Diabetic Retinopathy



Adapted from Sheetz MJ, King G. *JAMA*. 2002;288:2579-2588.

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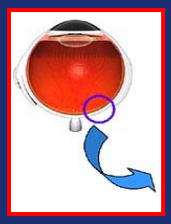
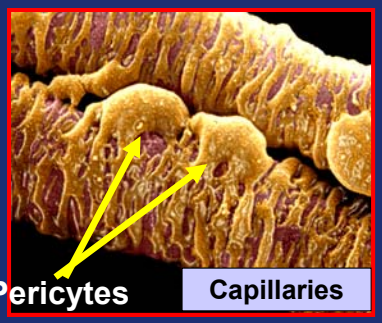
Anatomy: Close-up View of Retinal Capillaries





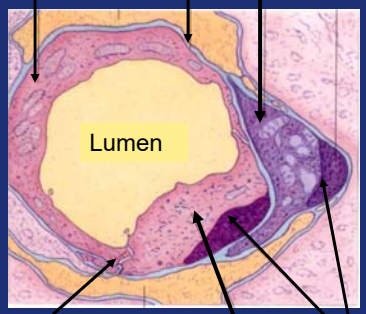


Image L: Available at: http://www.udel.edu/Biology/Wags/b617/stereo/stereo9.gif.

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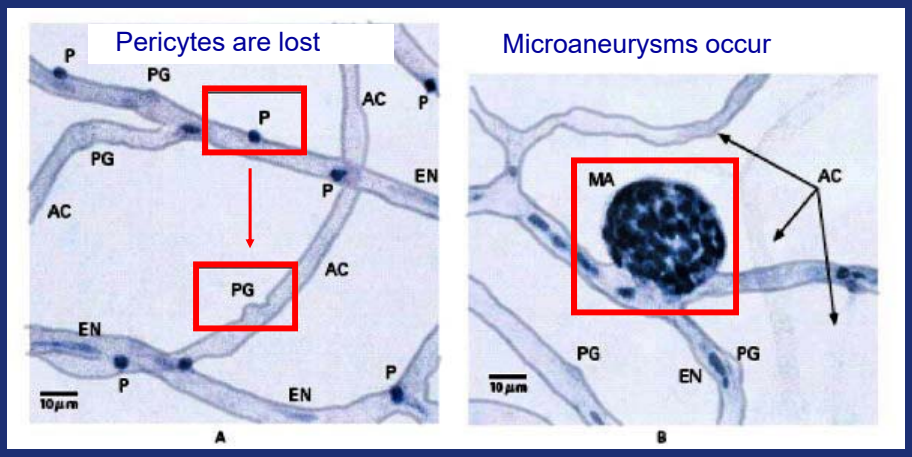
Loss of Pericytes and Microaneurysms: Mild Diabetic Retinopathy



P= Pericytes PG= Pericyte "ghosts" EN= Endothelial cells MA= Microaneurysm

Adapted from Ferris F, et al. *New Engl J Med.* 1999:341;667-678.

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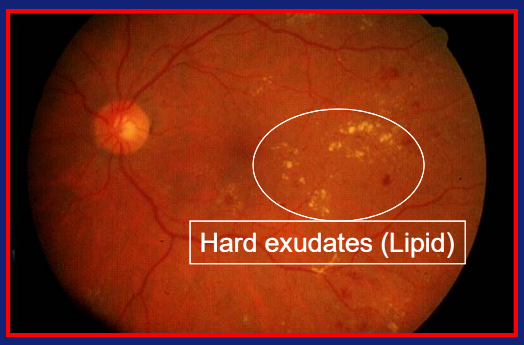
Nonproliferative Diabetic Retinopathy (NPDR): Clinical Features

- Clinical features:
  - microaneurysms
  - intra-retinal hemorrhages
  - cotton wool spots
  - hard exudates
  - venous tortuosity or beading
  - intraretinal microvascular abnormalities (IRMA)[1,2]



- Increased vascular permeability of retinal capillaries may result in Diabetic macular edema (DME)[1,2]

1. Ciulla TA, et al. *Diabetes Care.* 2003;26(9):2653-2664. 2. American Academy of Ophthalmology. Diabetic Retinopathy Preferred Practice Pattern®: Diabetic retinopathy. Available at: http://www.aao.org/education/library/ppp/upload/Diabetic-Retinopathy.pdf. Accessed August, 2006.

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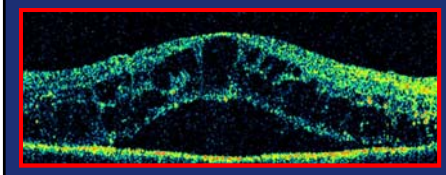
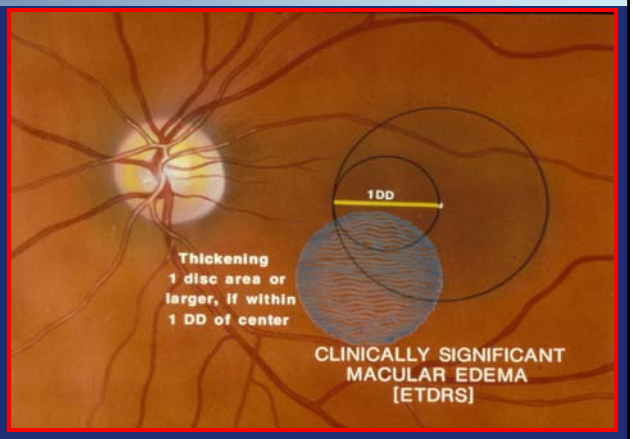
Clinically Significant Macular Edema (CSME): Primary Cause of Vision Loss in DR

- Definition: permeability, leakage, and accumulation of intraretinal fluid[1]
- Lipid exudates from damaged retinal capillaries and microaneurysms[1]





Macular edema may occur at any stage of retinopathy[2]
Leading cause of vision loss in patients with type 2 diabetes[2]

1. Available at: visionfordiabetes.com 2. Ciulla TA, et al. *Diabetes Care.* 2003;26:2653-2664.

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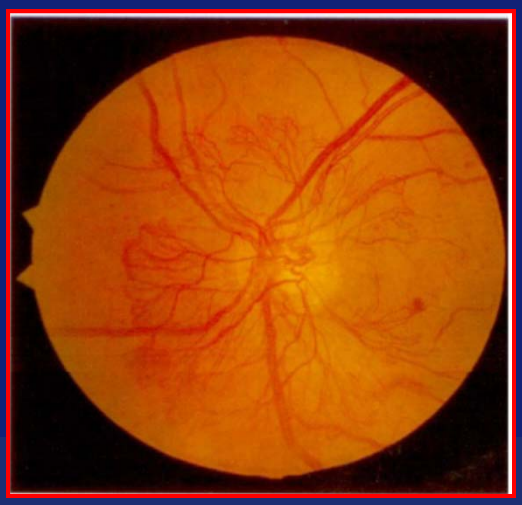
Proliferative Diabetic Retinopathy (PDR): Important Cause of Blindness

Pathology: Stimulated by ischemic changes in the retina in response to vaso-occlusive effects of hyperglycemia on retinal microvasculature[1]

Anatomical changes:[2]
- Neovascularization
- Pre-retinal or vitreous hemorrhage
- Fibrous tissue proliferation
- Traction retinal detachment

Risk: 50% chance of blindness within 5 years, if PDR is not treated[3]



1. Flynn HW, Smiddy WE. *Diabetes and Ocular Disease: Past, Present, and Future Therapies*. San Francisco: The Foundation of the AAO; 2000.
2. Fong DS, et al. ETDRS Research Group. *Am J Ophthalmol* 1999;127:137-141.
3. Ferris F, et al. *New Engl J Med.* 1999:341;667-678.

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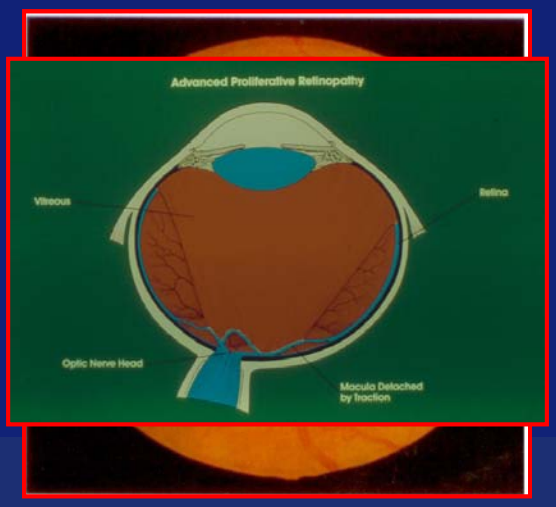

1. Flynn HW, Smiddy WE. *Diabetes and Ocular Disease: Past, Present, and Future Therapies*. San Francisco: The Foundation of the AAO; 2000.
2. Fong DS, et al. ETDRS Research Group. *Am J Ophthalmol* 1999;127:137-141.
3. Ferris F, et al. *New Engl J Med.* 1999:341;667-678.

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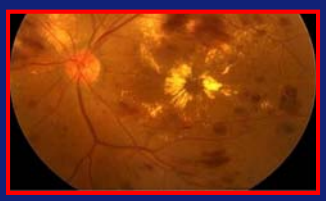
Vision Loss from Diab Retinopathy Results Mainly from 2 Causes: Leakage and Ischemia[1,2]

Leakage
↓
Hemorrhage, Exudates
Vascular Leakage
↓
NPDR
Clinically Significant Macular Edema



Ischemia
↓
Neovascularization
↓
Proliferative DR

May result in vision loss or blindness

1. American Academy of Ophthalmology. Diabetic Retinopathy Preferred Practice Pattern. Available at: http://www.aao.org/education/library/ppp/upload/Diabetic-Retinopathy.pdf. Accessed September, 2006.
2. Ciulla TA, et al. *Diabetes Care.* 2003;26:2653-2664.

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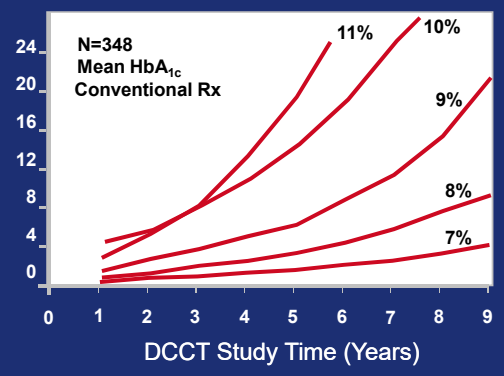
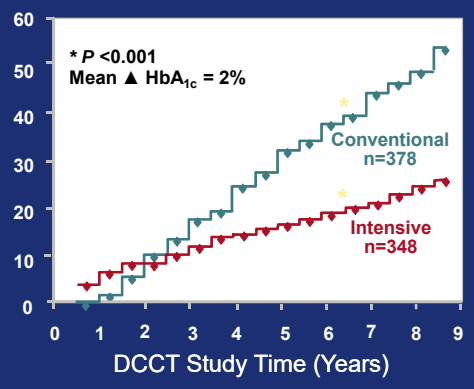
DCCT: Effect of Blood Glucose Control on Progression of Retinopathy in Type 1 Diabetes

Rate of Retinopathy Progression by HbA_{1c}
Events per 100 Person-years



Cumulative Incidence of DR Change
% of Patients



Secondary Prevention: Patients with type 1 diabetes and mild retinopathy at base line;
Progression = 3 steps on ETDRS scale sustained for at least 6 months.

Adapted from: DCCT Research Group. *Diabetes*. 1995;44:96-983.

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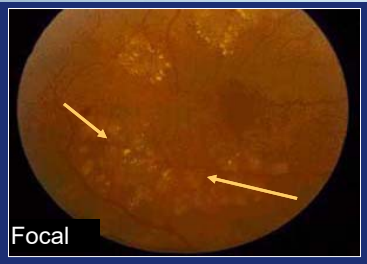
Treatment Options: Laser Photocoagulation

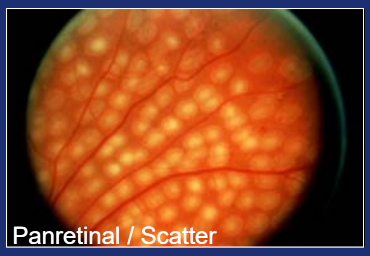
Focal or Grid Photocoagulation

- Treats Diabetic Macular Edema
- Focal PC: light, small-sized burns to leaking microaneurysms
- Grid PC: a grid of burns to areas of edema from capillary leakage or nonperfusion
- Results: 50% reduction in moderate visual loss



Panretinal Photocoagulation

- Treats Proliferative Diabetic Retinopathy
- Indirectly treats neovascularization by placing laser burns throughout the peripheral fundus
- Results: 50% reduction in severe visual loss



1. AAO. 2003. Preferred Practice Pattern®: Diabetic retinopathy. 2003. 2. ETDRS Research Group. *Ophthalmology*. 1991;98(5 suppl):766-785.

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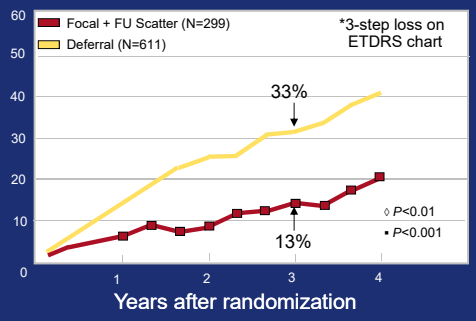
Laser Photocoagulation: Efficacy

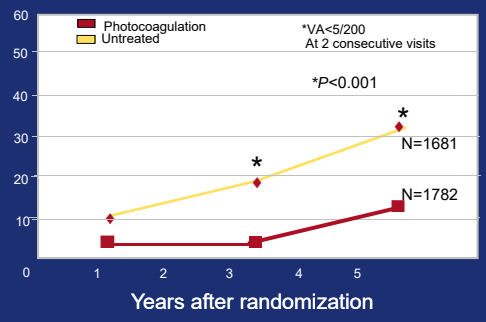
In Mac Edema and Less Severe DR[1]
% of Patients with Moderate Visual Loss



Outcomes in Macular Edema:

- 50% reduction in moderate visual loss
- Increased chance of mod visual gain
- Reduced retinal thickening

In PDR[2]
% of Patients with Severe Visual Loss



Outcomes in Proliferative DR:

- 50% reduction in severe visual loss
- Indicated only for severe PDR

1. ETDRS. *Arch Ophthalmol*. 1995;113:1144-1145. 2. DRS. *Ophthalmology*. 1978;85:82-106.

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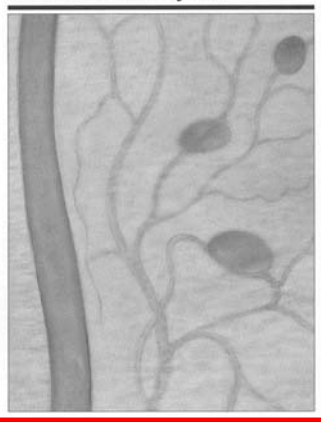
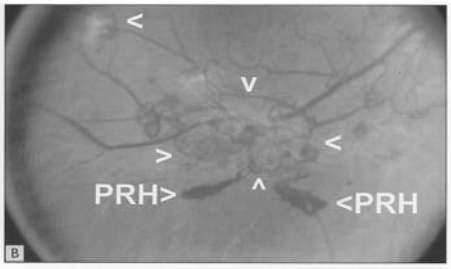
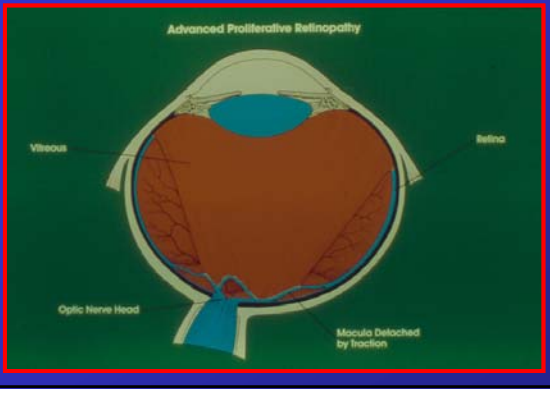
Diabetic Retinopathy

Retinal Microaneurysms

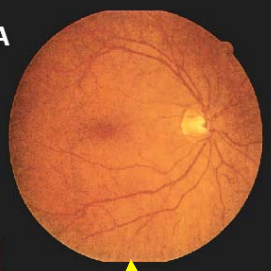


Retinal Neovascularization

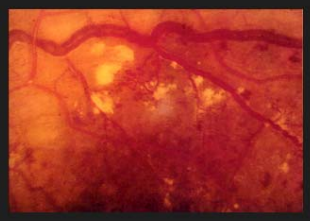




Diabetic Retinopathy

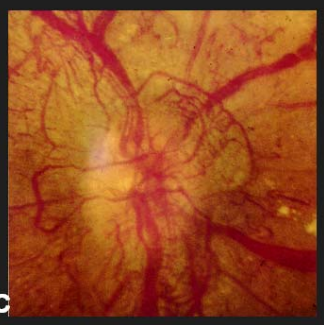


Microaneurysms
Exudates
Venous Dilatation



Pericytes:
Oxidation
Cell Death
Endothe Dys
Ischemia
VEGF

Proliferative Retinopathy:
Fibrosis
Distortion of the vitreous
Tearing of the retina

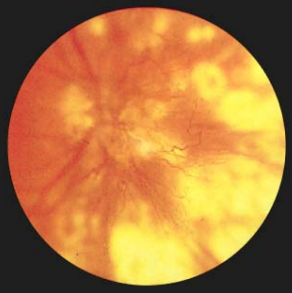


Hall R, et al. Diabetes mellitus. In: *A Colour Atlas of Endocrinology*. 2nd ed. 1990:chap 7.

Diabetic Retinopathy

Vitreous
Hemorrhage

Laser
Burns



Hall R, et al. Diabetes mellitus. In: *A Colour Atlas of Endocrinology*. 2nd ed. 1990:chap 7.

Diabetic Neuropathies

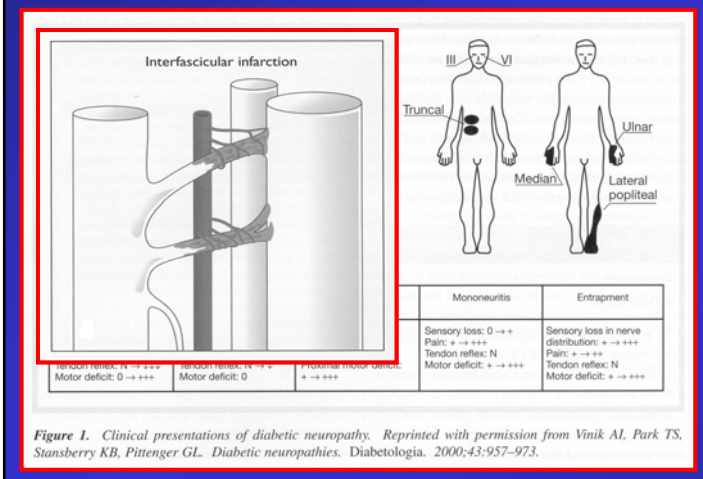
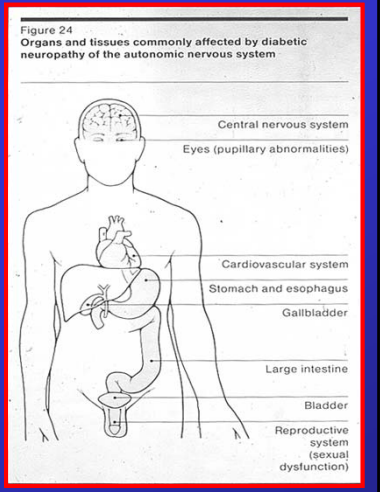
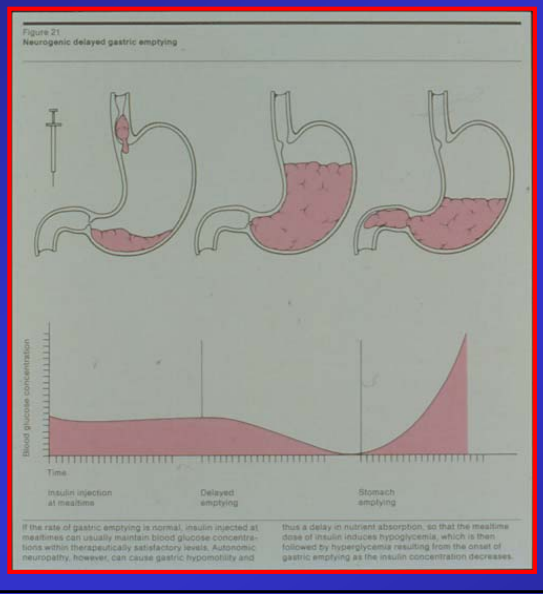


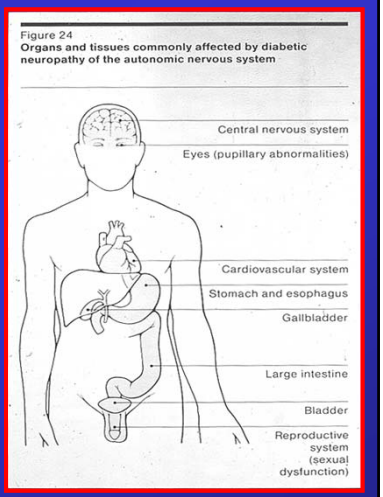
Figure 1. Clinical presentations of diabetic neuropathy. Reprinted with permission from Vinik AI, Park TS, Stansberry KB, Pittenger GL. Diabetic neuropathies. Diabetologia. *2000;43:957–973.*



Nerve Damage: Vasculitis, demyelination, remyelination, cell death

Diabetic Neuropathies

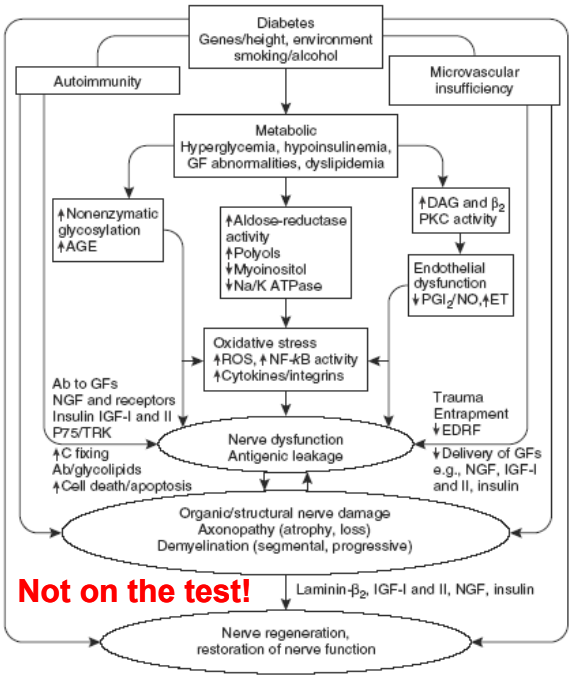




Diabetic Neuropathies

Theories:

1) Metabolic
   Glucose, polyol, sorbitol, lipids, GLA, carnitine, AGE, growth factors
2) Immune
   autoantibodies: PL, gangliosides
3) Microvascular
   vasoconstriction
4) Neurotropic: loss of neurotrophins, growth factors
5) Oxidative stress
6) Infarction - atherosclerosis
7) Entrapment



Not on the test!

The Diabetic Foot

A

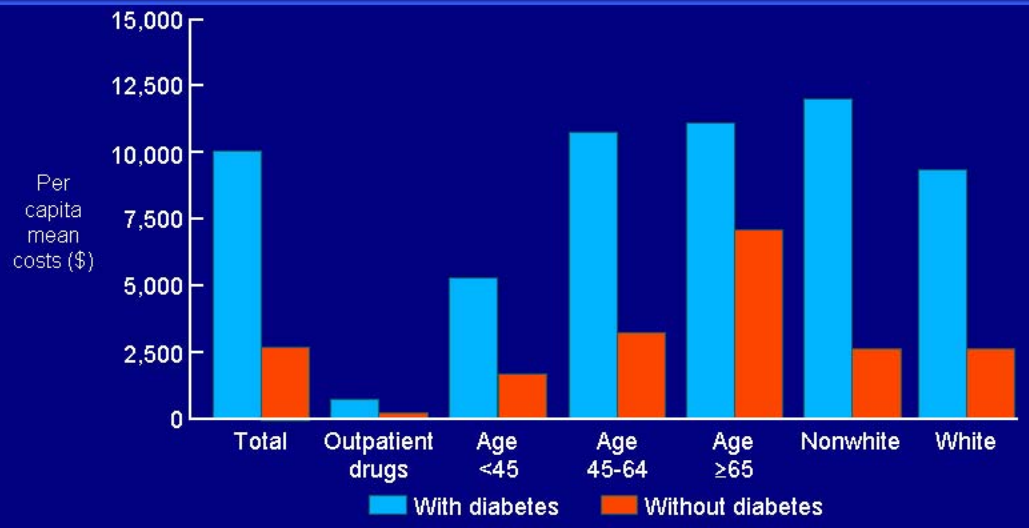
B

C

Hall R, et al. Diabetes Mellitus. In: *A Colour Atlas of Endocrinology*. 2nd ed. 1990:chap 7.

Diabetic Neuropathies

Per Capita Expenditures by Demographic Characteristics, 1997



1.18 ©1998 PPS

American Diabetes Association. *Diabetes Care*. 1998;21:296-309.

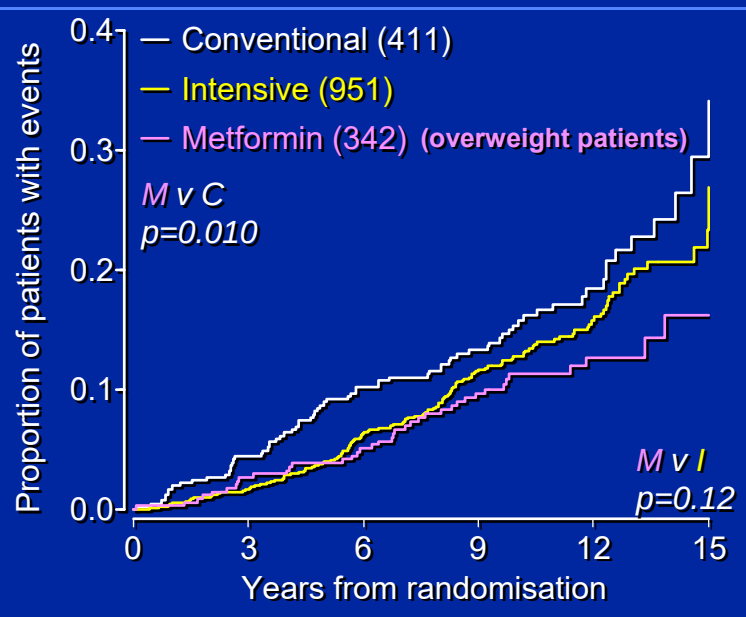
Diabetes Mellitus:

Multiple Pathways to Cardiovascular Events

Therapy for Atherosclerosis

(NOT on the TEST)

Myocardial Infarction



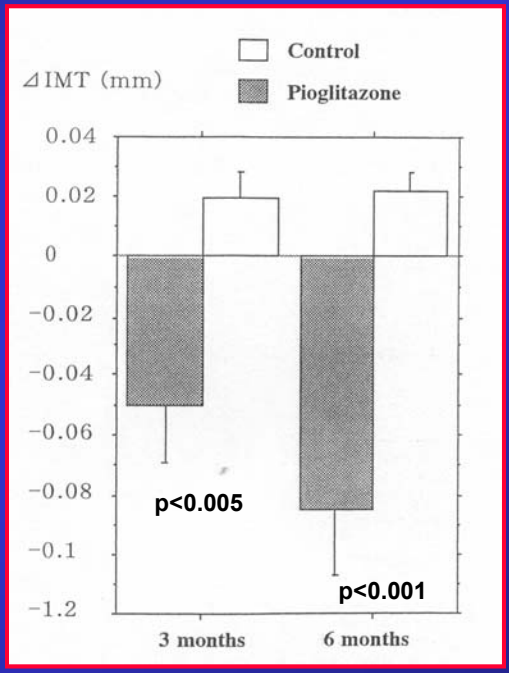
ukpds

Pioglitazone
Carotid Ultrasound

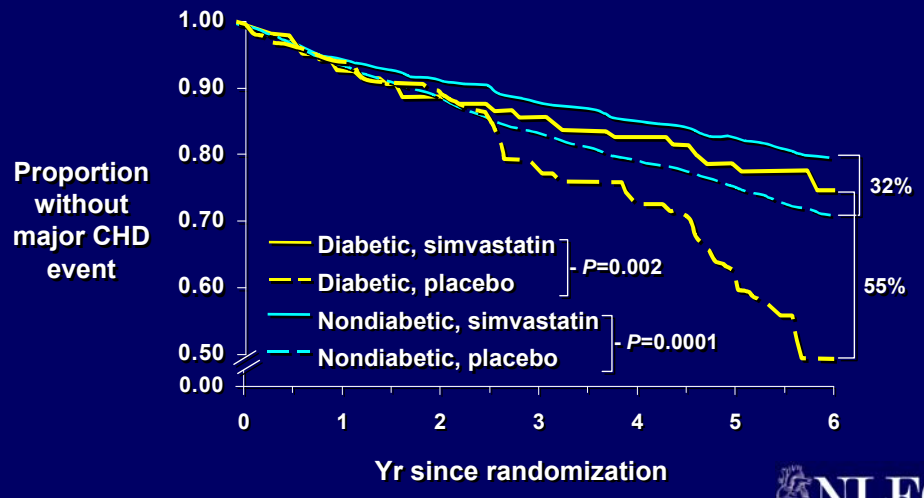
106 Japanese with Type 2 DM
Randomized: Pio 30 mg or Plac
Age: 62.2 ± 1.1 yrs
Gender: ~ 55% male

Sulfonyureas: almost all
Statins: ~45%
Aspirin: none

HgbA1c: 8.5 --> 7.5 --> 7.3%
in Pio group
No change: Chol, TG, HDL, BP



4S: Major CHD Event Reduction in a Subgroup of Patients With Diabetes



Pyörälä K et al. *Diabetes Care*. 1997;20:614-620.

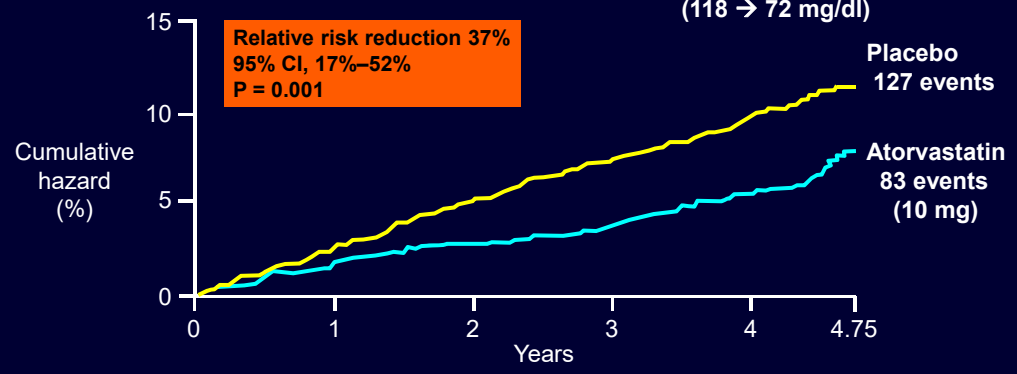
NLEC™

VBWG

CARDS: 37% Reduction in primary outcome

Type 2 DM (N = 2838)

LDL-C: Average difference 40% (118 → 72 mg/dl)



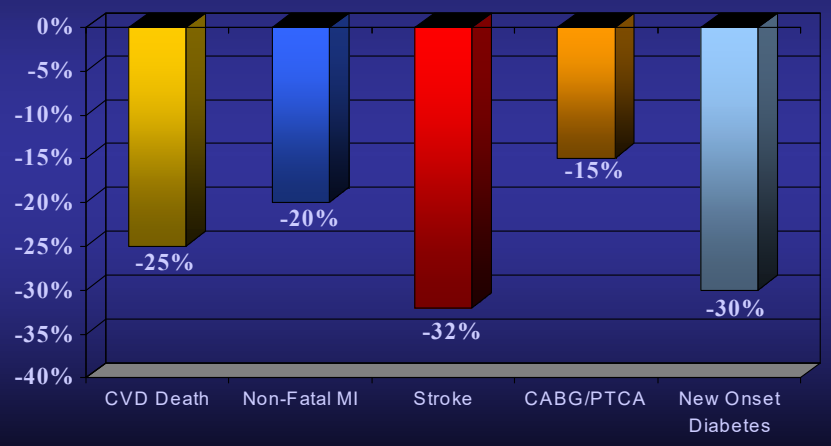
Placebo	1410	1351	1306	1022	651	305
Atorvastatin	1428	1392	1361	1074	694	328

Primary outcome: Composite of major coronary events, revascularizations, unstable angina, resuscitated cardiac arrest, and stroke

Colhoun HM et al. *Lancet*. 2004;364:685-96.

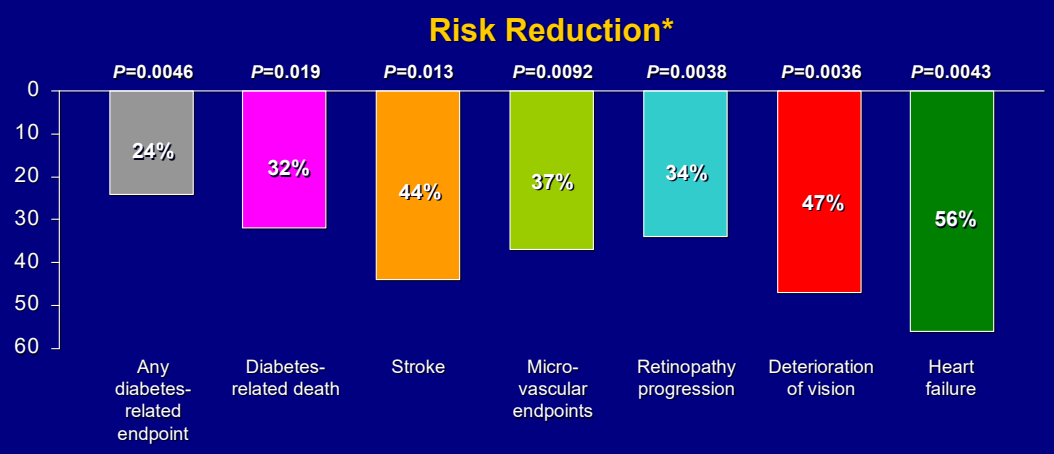
HOPE Trial: Risk Reduction (Ramipril vs Placebo)

Presented at 1999 ESC Meeting, August 31, 1999, Barcelona, Spain.



N=9541: (+) CVD, Diabetes, or multi risk factors; 4-year follow-up

UKPDS Results: Tight Blood Pressure Control

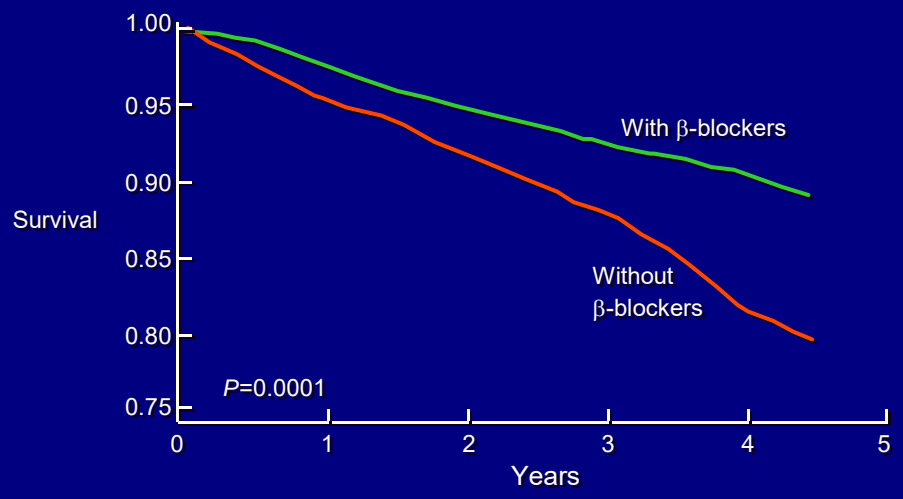


*Compared with less tight control. Captopril and atenolol were equally effective in reducing risk and were equally safe in patients with diabetes.

III.51

UKPDS Group. *BMJ.* 1998;317:703-713.

β-Blocker Treatment Improves Survival of Patients With Diabetes: The BIP* Study



*Bezafibrate Infarction Prevention

Jonas M et al. *Am J Cardiol.* 1996;77:1273-1277.

Atherosclerosis: Introduction

Impact of Diabetes (Types I & II) on Atherogenesis:

Metabolic - hyperglycemia, hyperinsulinemia
Chemical - glycation, oxidation

60

Goals: HgbA1c < 6.5% (< 5.5%?)

Lipoproteins, Apolipoproteins, and Lipids
LDL < 60, TG < 130, HDL > 50 mg/dl

Vessal Wall - cells, matrix, and contraction
BP < 120/75 (use TZD, ACE-I, beta-blockers)

Coagulation - platelets, clottings factors, and fibrinolysis
Aspirin, TZD, Statins, Omega 3, Stop Smoking

Neovascularization
Daily Exercise, Wt Loss, Low Carbs, Myr, & Palm