Pathogenesis of Diabetic Macrovascular Complications

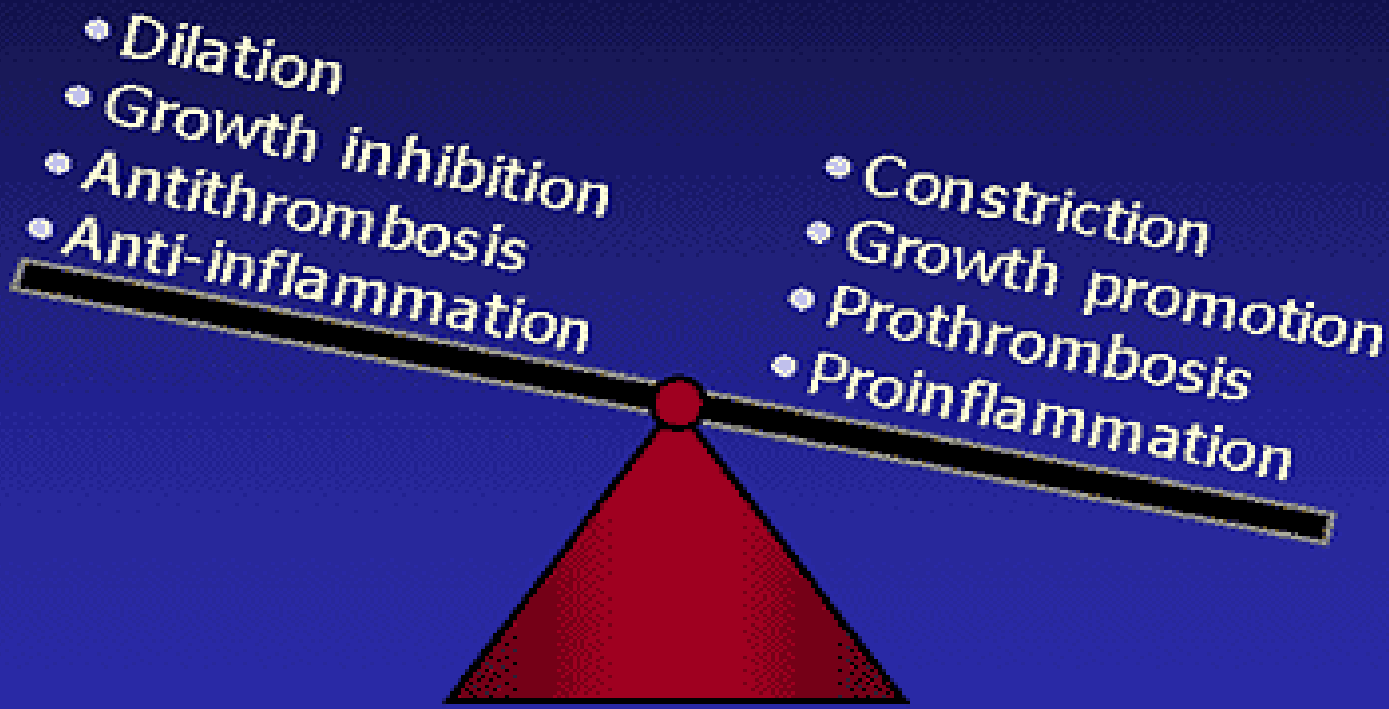
부산의대 내과학교실
김 인 주

Macrovascular disease in Type 2 diabetes

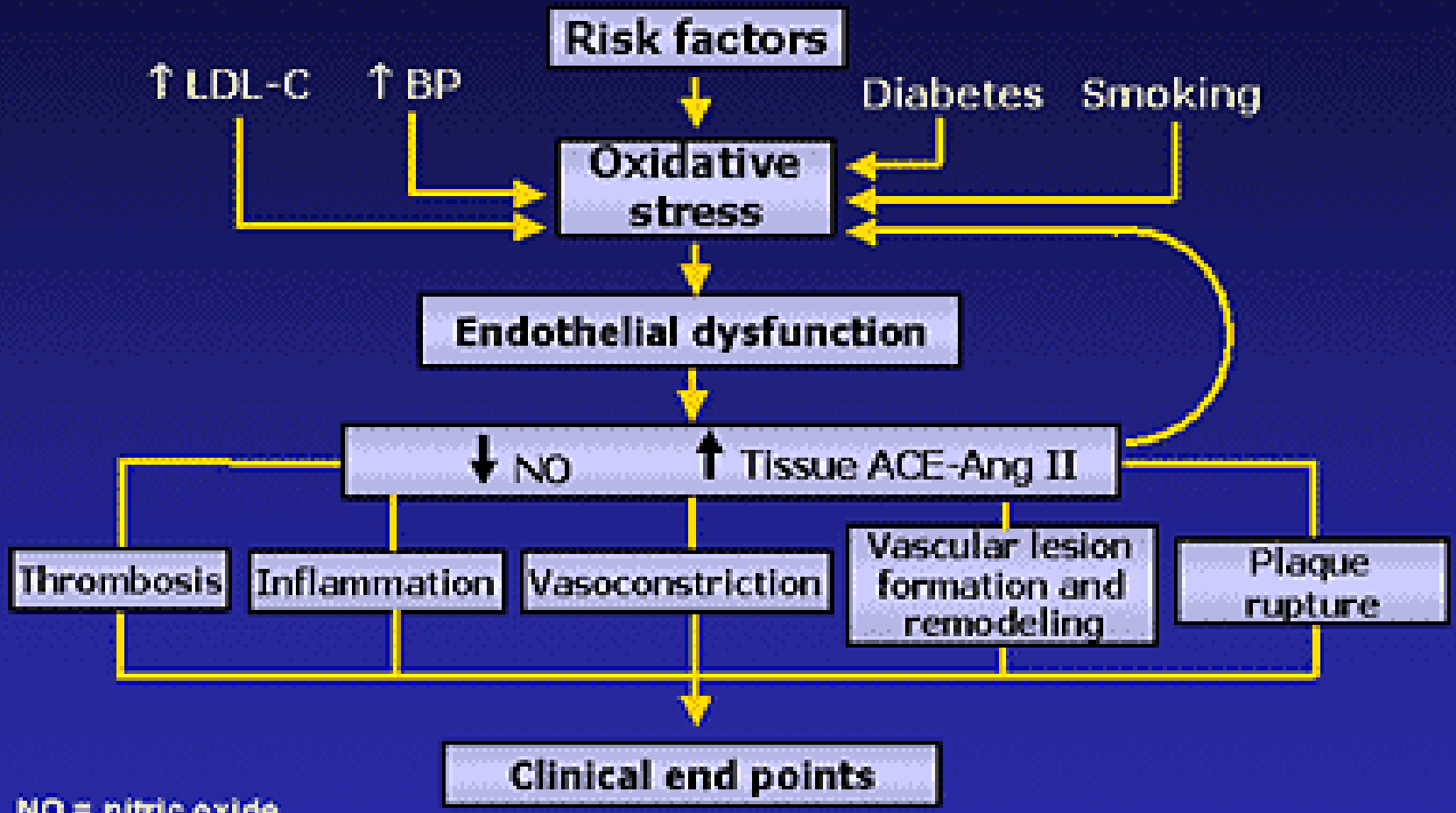
Krolewski AS et al. *Am J Med.* 1991;90(suppl 2A):56S-61S.

Atherosclerosis Timeline

Endothelial Dysfunction



The Progression From CV Risk Factors to Endothelial Injury and Clinical Events

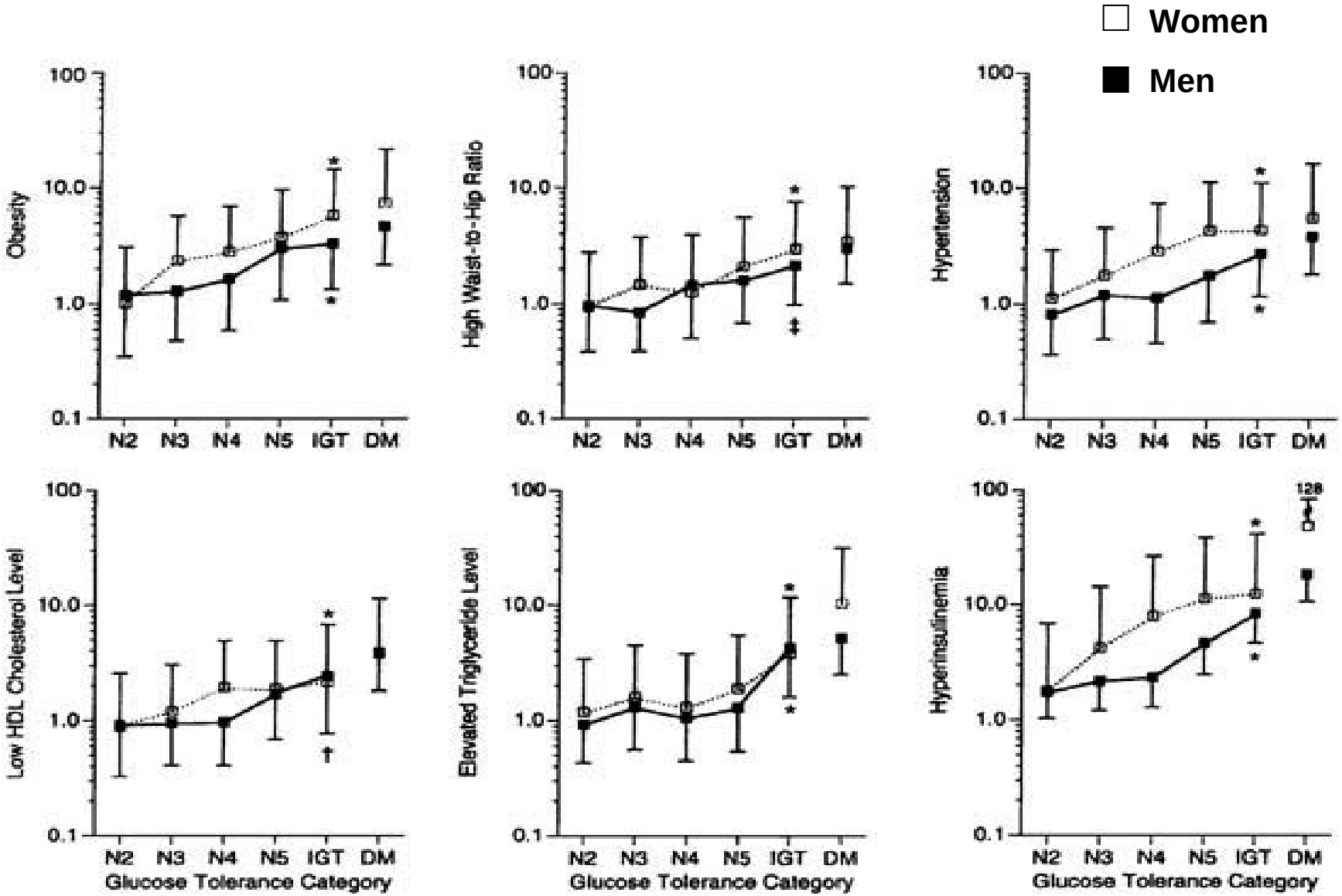


NO = nitric oxide

Adapted from Gibbons GH, Dzau VJ. *N Engl J Med.* 1994;330:1431-1438.

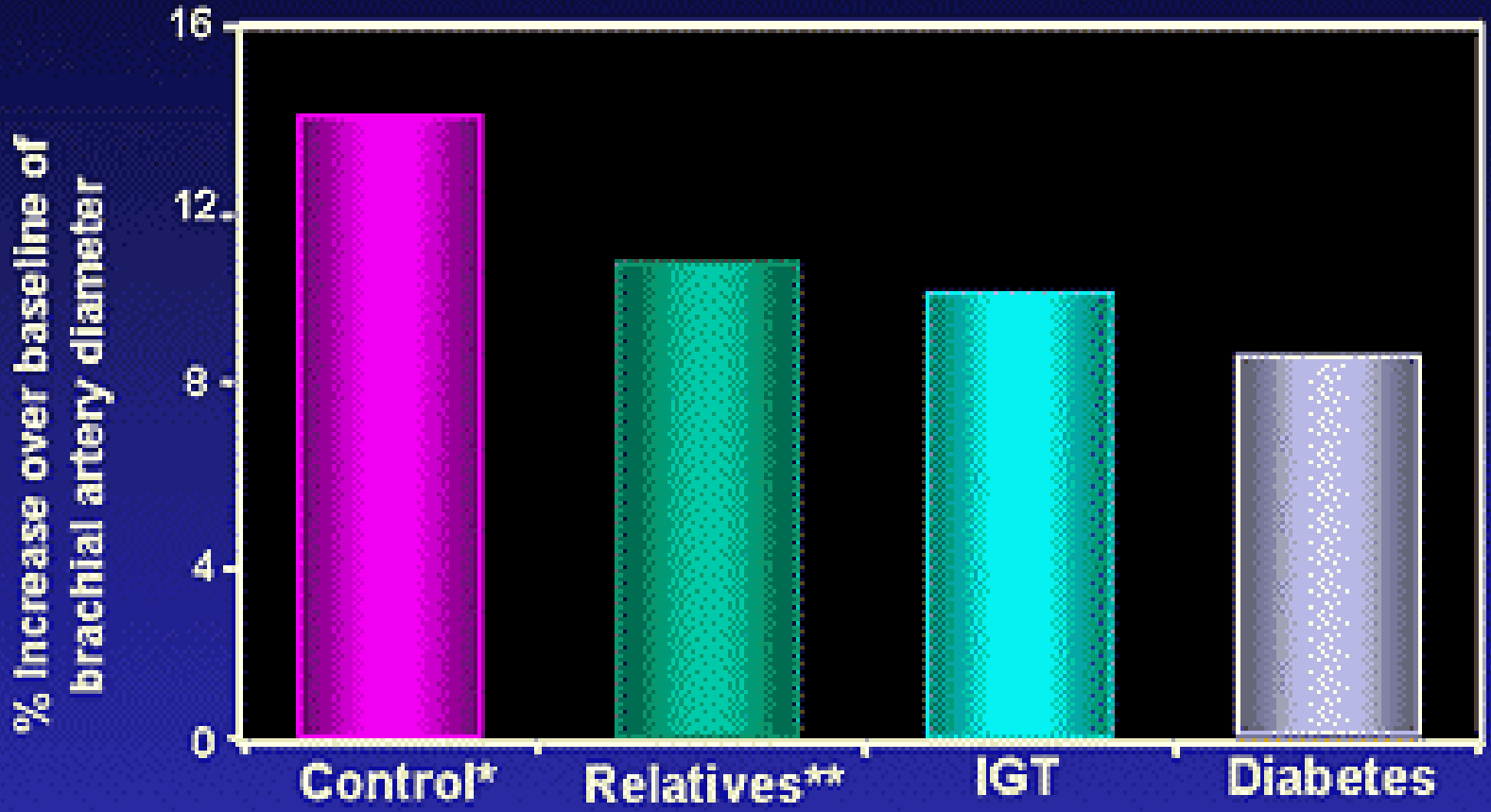
Factors Underlying Accelerated Atherogenesis in DM

- Diabetic dyslipidemia
  - ↑ TG-rich LPs, ↓ HDL, ↑ small, dense LDL
- Hyperglycemia
  - Glyco-oxidation, sorbitol/myoinositol pathway, Diacylglycerol/PKC activation
- Hypertension
- Oxidative stress
- Hemorrheological alterations
  - ↑ platelet aggregation, fibrinogen, PAI-1
  - ↓ fibrinolysis
- Endothelial dysfunction
- Insulin resistance
- Others
  - Sympathovagal imbalance, vascular inflammation, etc



Metabolic risk factors worsen continuously across the spectrum of nondiabetic glucose tolerance. The Framingham Offspring Study. Ann Int Med 1998;128:524–533

Impaired Endothelium-Dependent Vasodilation in People at Risk for Type 2 Diabetes

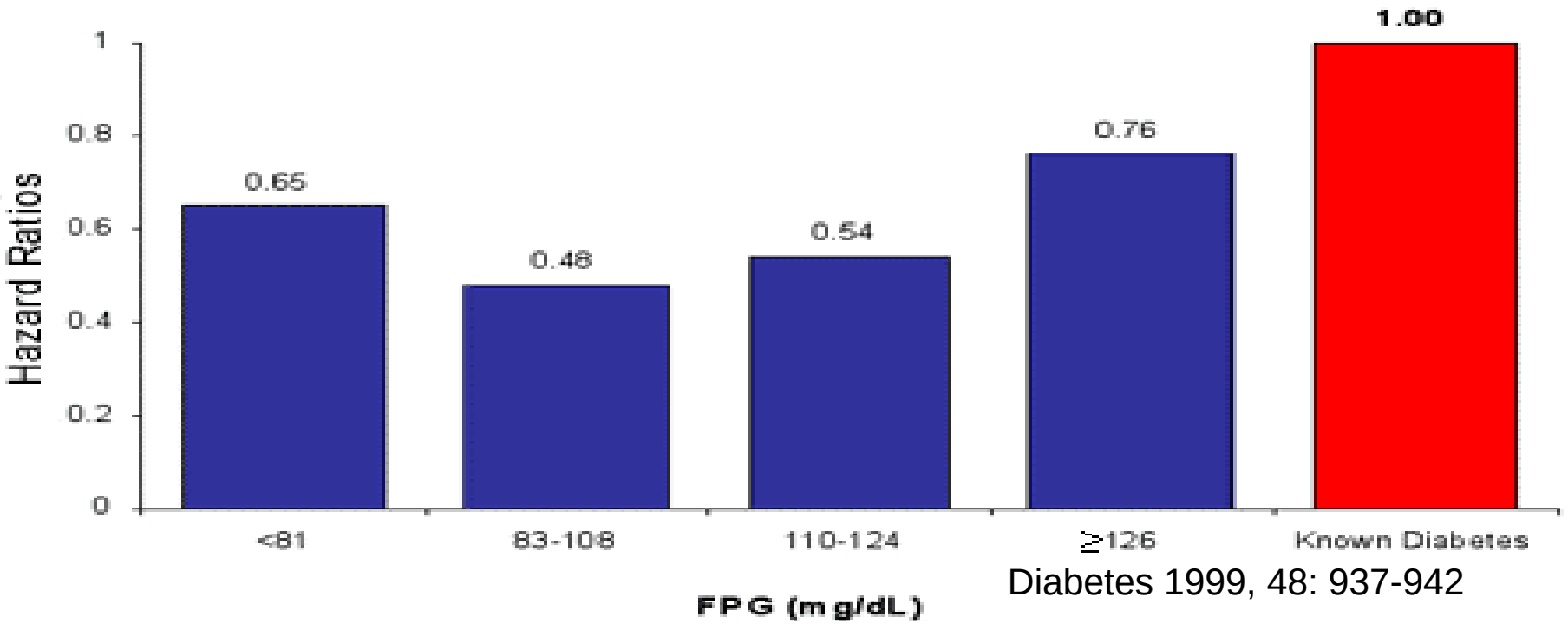


*C vs R, IGT, D
**1 or both parents

Caballero AE et al. *Diabetes*. 1999;48:1856-1862.

THRESHOLD OF GLUCOSE TO INCREASE THE RISK OF CARDIOVASCULAR COMPLICATIONS

Figure 2. Hazard ratios for CVD mortality in relation to FPG intervals using previously diagnosed diabetes as a common reference category, and population adjusted for age, sex, cohorts, BMI, systolic blood pressure, cholesterol, and smoking. Adapted from The DECODE Study Group.[4]

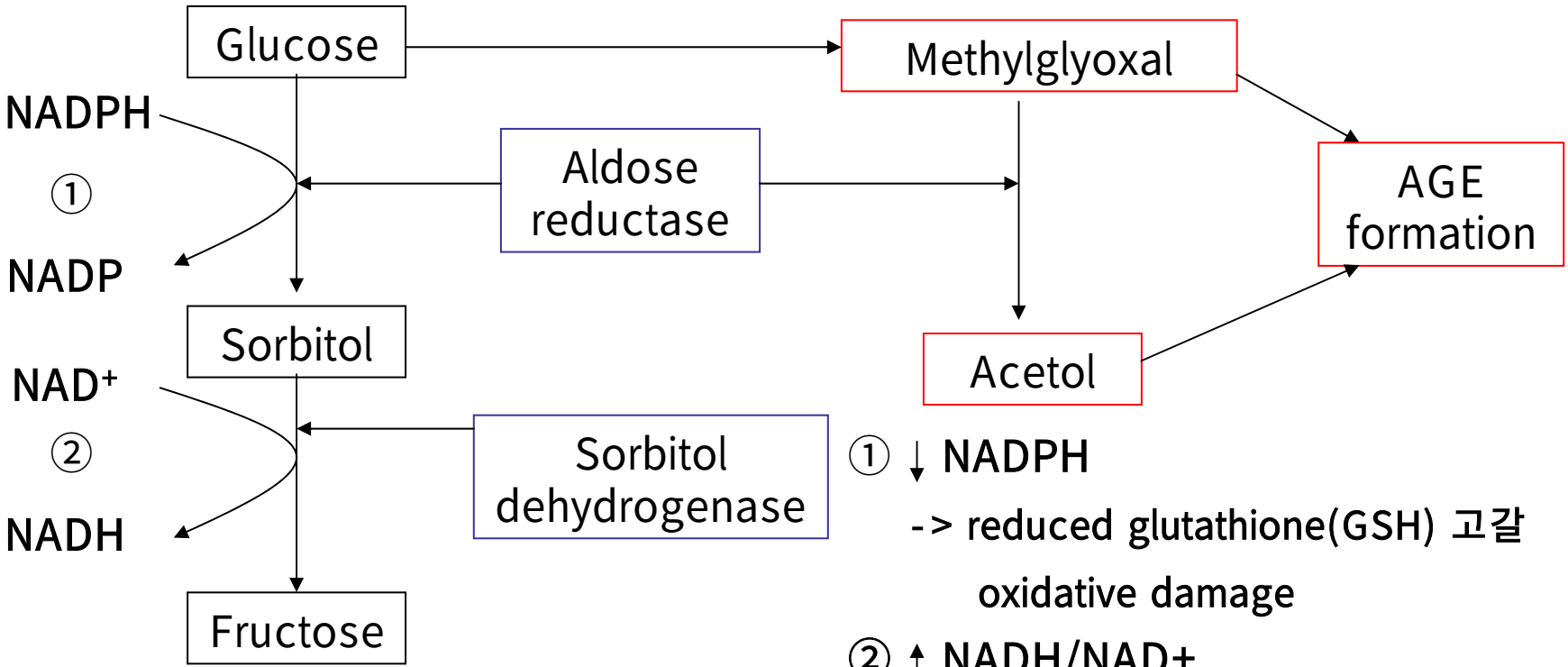


Diabetes 1999, 48: 937-942

Mechanisms of hyperglycemia-induced damage

- Increased flux of glucose and other sugars through the polyol pathway
- Increased intracellular formation of advanced glycation end-products(AGEs)
- Oxidative stress
- Activation of protein kinase C(PKC isoforms).
- Overactivity of the hexosamine pathway

Increased Polyol Pathway Flux



- Aldose reductase
  - –Normal person : relatively inactive
  - –Hyperglycemic state : increased flux

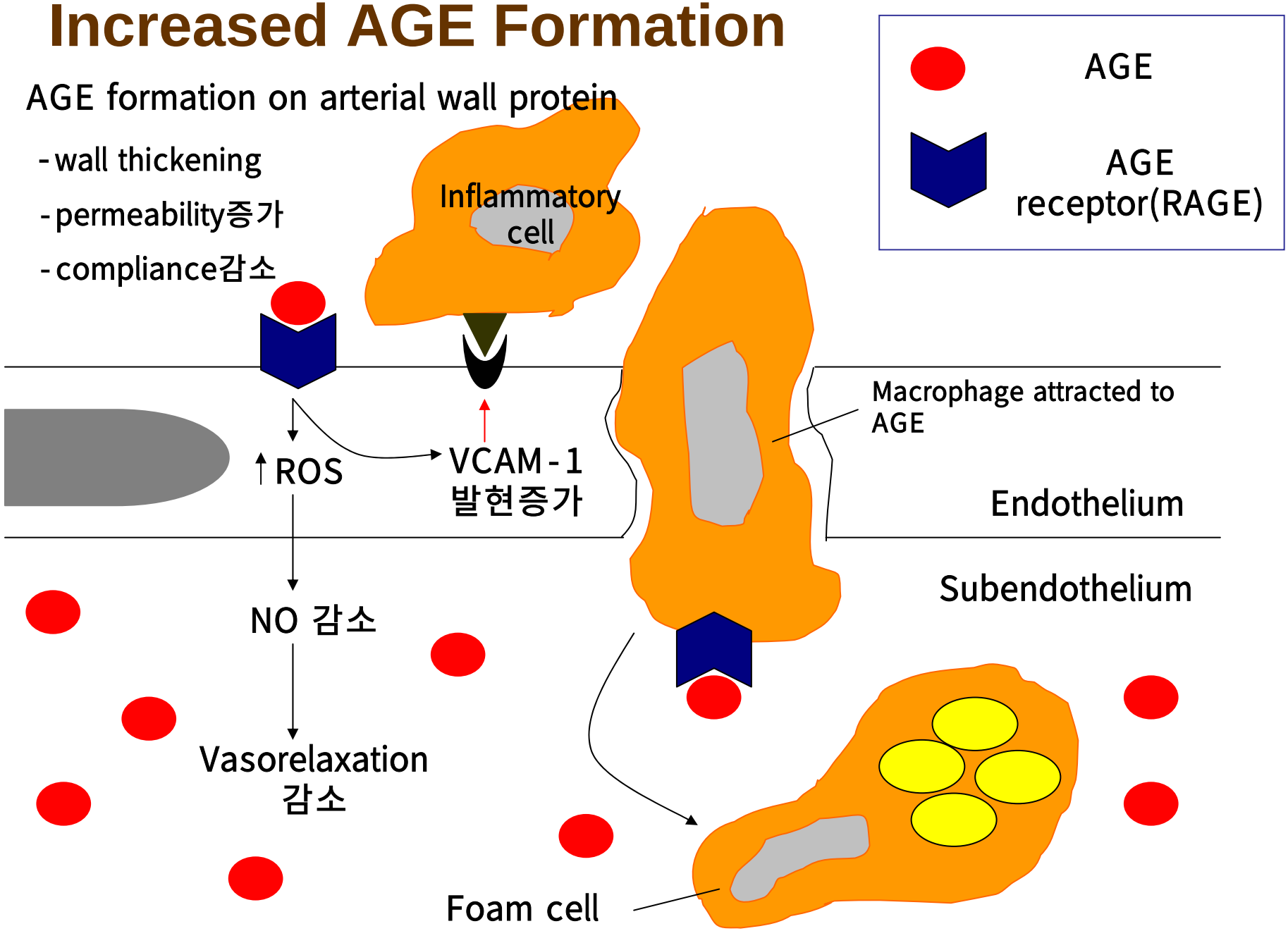
① ↓ NADPH
-> reduced glutathione(GSH) 고갈
oxidative damage

② ↑ NADH/NAD+
-> ↑Triose phosphate
(AGE formation)
PKC activation

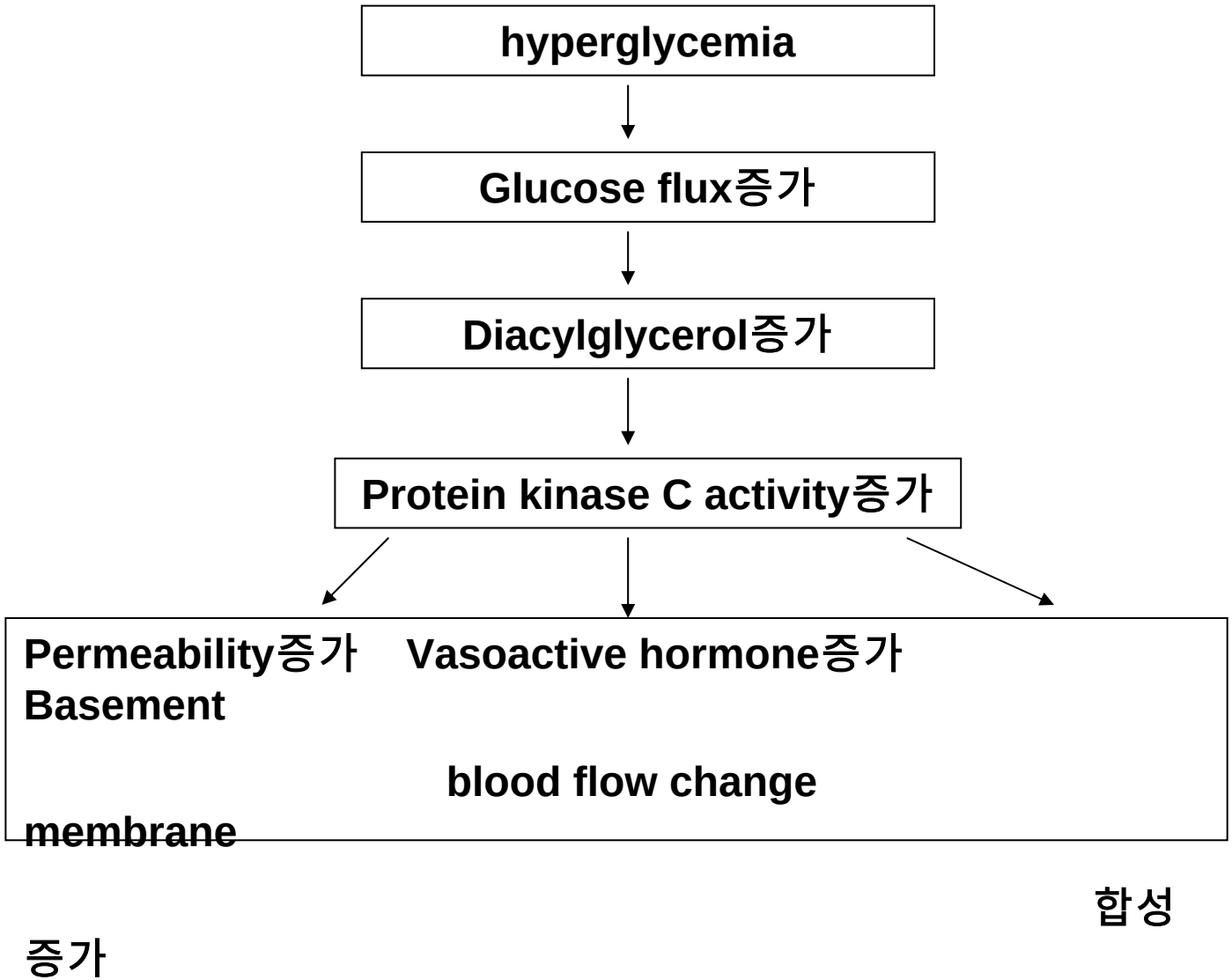
③ Decreased cytosolic Na^+/K^+ adenosine triphosphatase(ATPase)

④ Sorbitol-induced osmotic stress

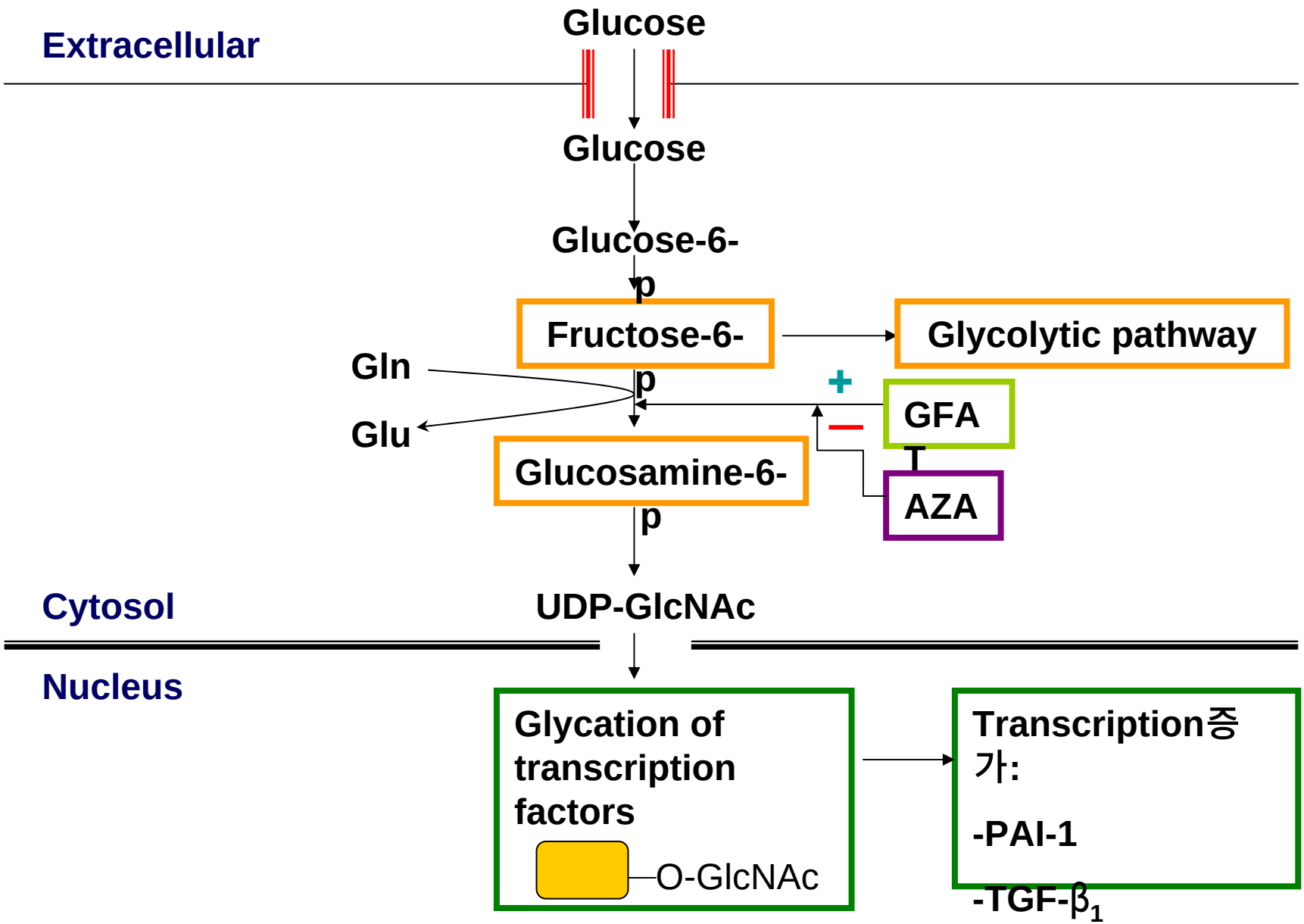
Increased AGE Formation



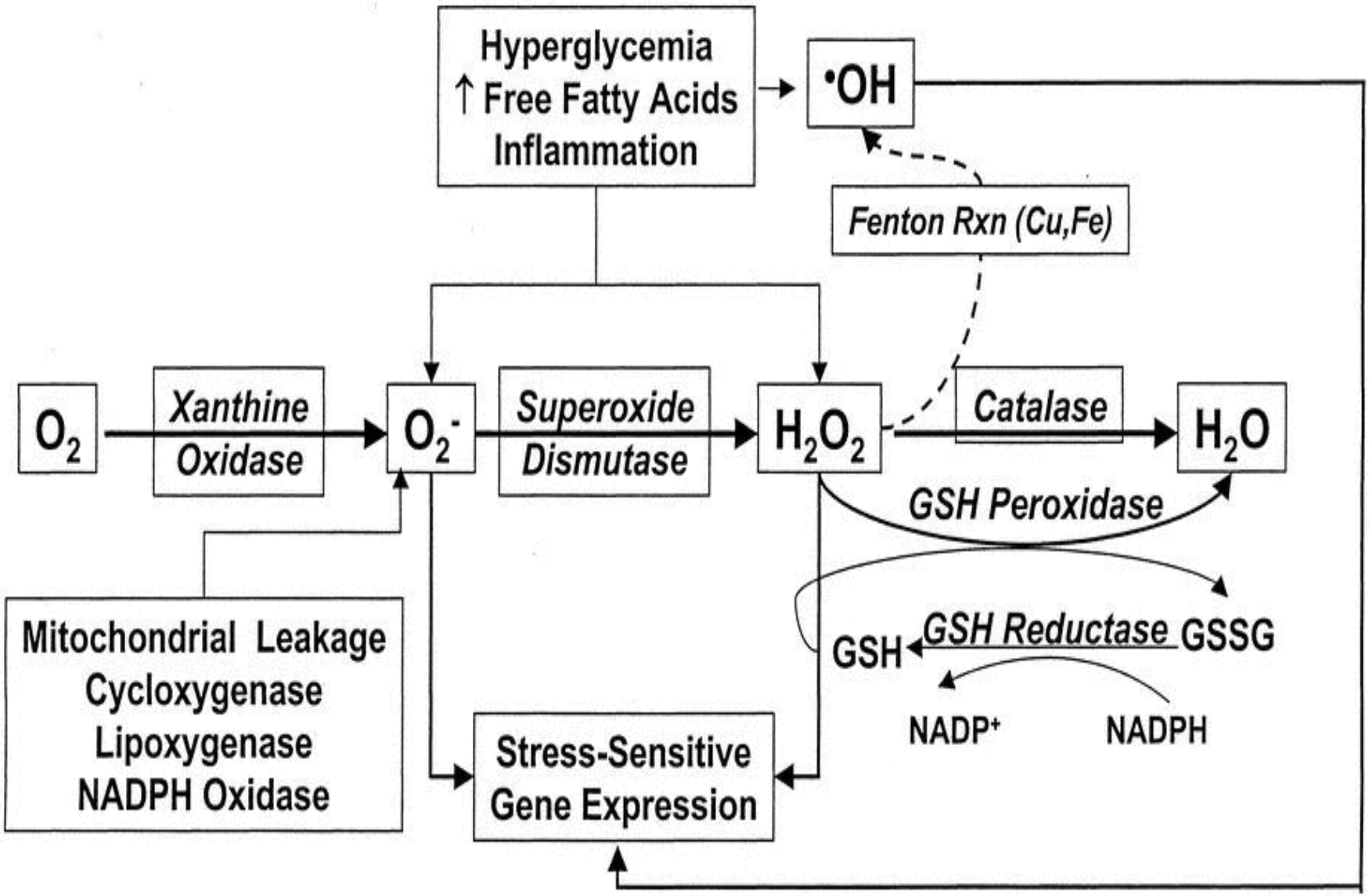
Increased protein kinase C activation



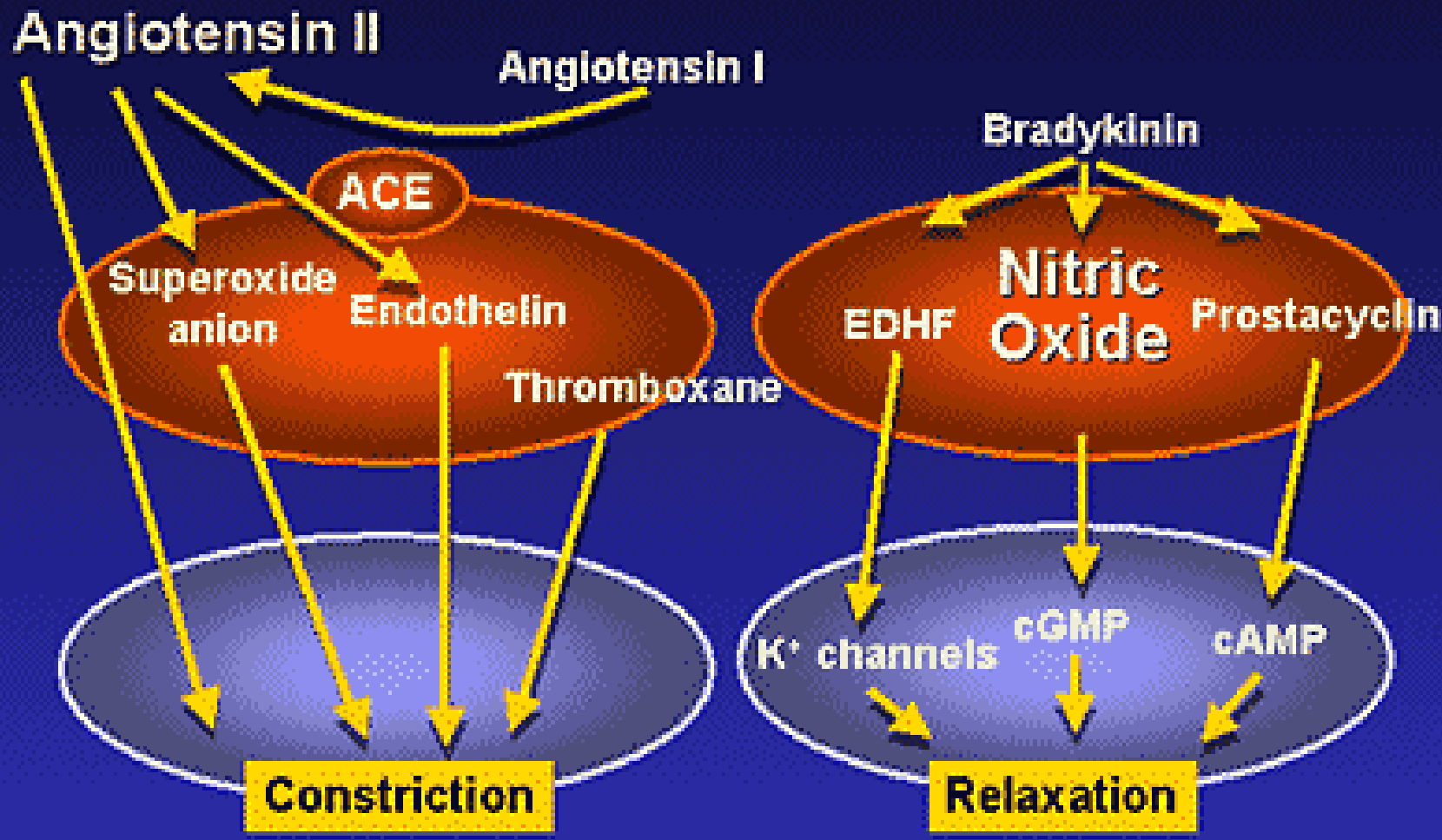
Increase hexosamine pathway



Oxidative stress



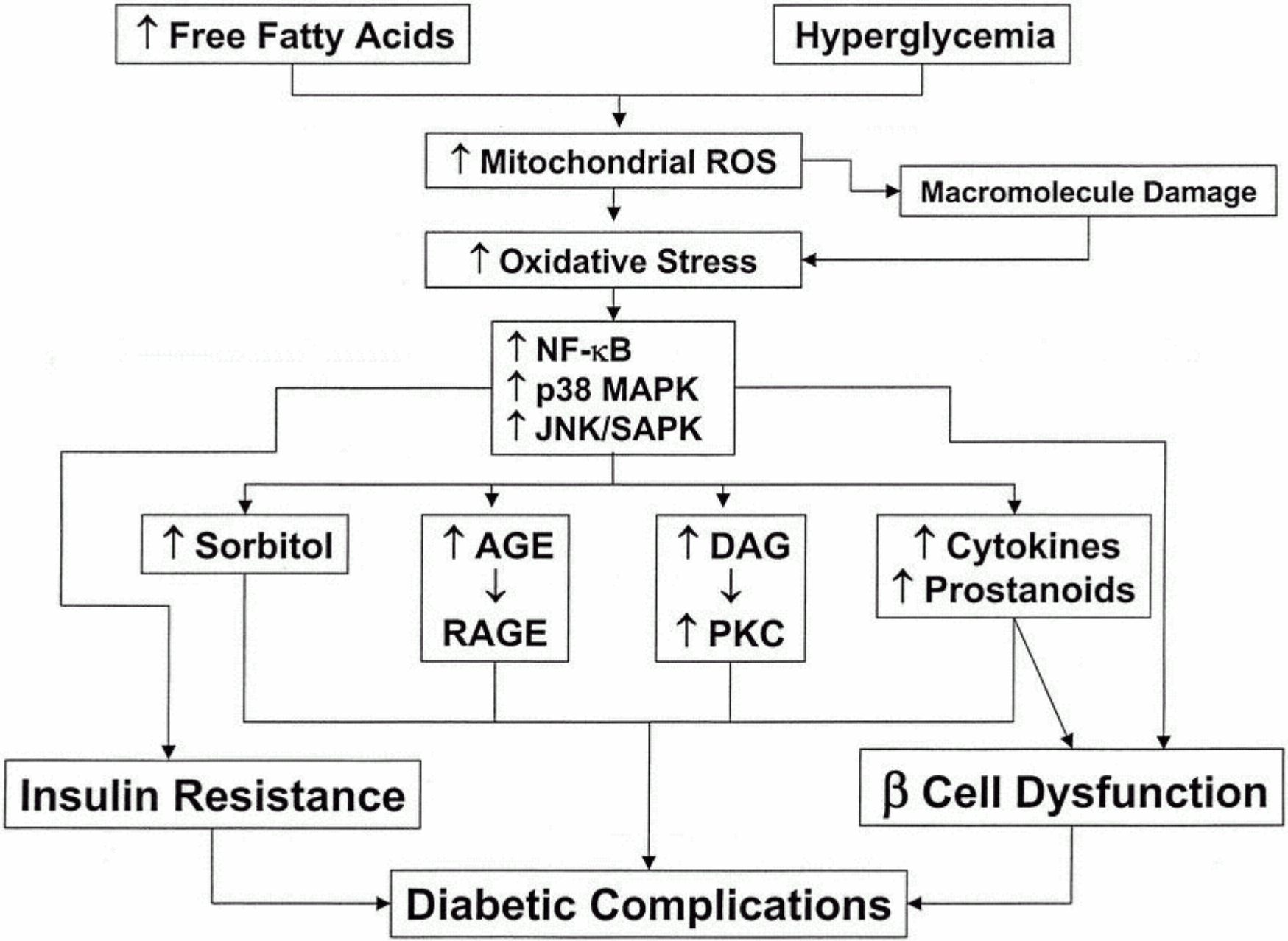
Regulation of Vascular Tone



EDHF=Endothelium Derived Hyperpolarizing Factor

Biochemical pathways in diabetic Cx

- Stress-sensitive pathways
  - nuclear factor-[kappa]B (NF-[kappa]B)
  - p38 MAPK
  - NH_2-terminal Jun kinases/stress-activated protein kinases (JNK/SAPK)
- AGE/RAGE pathway
- PKC pathway
- Polyol pathway
- Hexosamine pathway


↑ Free Fatty Acids
Hyperglycemia
↑ Mitochondrial ROS
Macromolecule Damage
↑ Oxidative Stress
↑ NF-κB
↑ p38 MAPK
↑ JNK/SAPK
↑ Sorbitol
↑ AGE
↓
RAGE
↑ DAG
↓
↑ PKC
↑ Cytokines
↑ Prostanoids
Insulin Resistance
β Cell Dysfunction
Diabetic Complications

배양된 토끼 혈관 내피세포의 기능에 대한 고농도 포도당의 효과

- 대한당뇨병학회지 21권 2호 156 ~ 167, 1997

중성구의 혈관 내피세포 부착에 대한 포도당의 효과에 관한 연구

- 대한당뇨병학회지 21권 3호 262 ~ 270, 1997

내피세포의 adhesion molecule 발현에 미치는 고농도 포도당의 효과

- 대한당뇨병학회지 22권 3호 280 ~ 289, 1998

산화 저비중지단백이 중성구의 부착과 이동에 미치는 효과

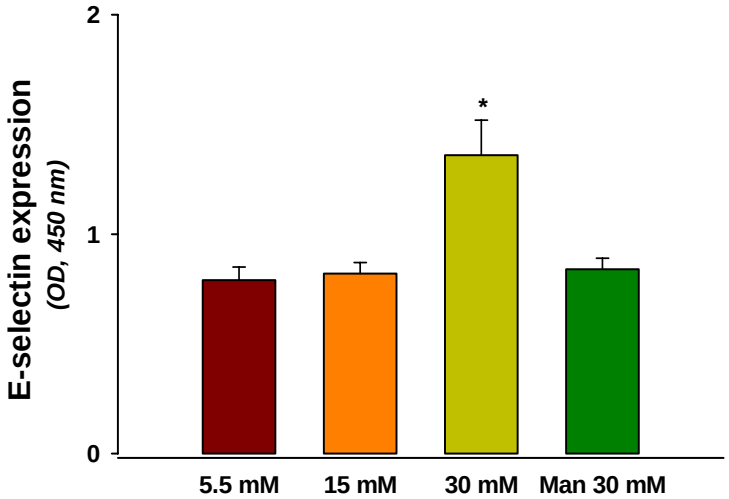
- 대한당뇨병학회지 23권 1호 12 ~ 24, 1999

고농도 포도당조건에서 호중구에 의한 내피세포의 손상에 관한 연구

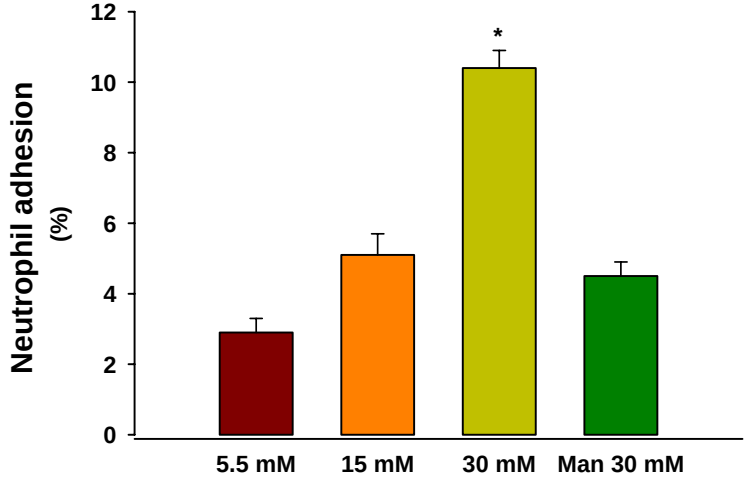
- 대한당뇨병학회지 24권 6호 652 ~ 665, 2000

OLETF 쥐에서 내피세포 의존성 혈관이완 장애의 기전

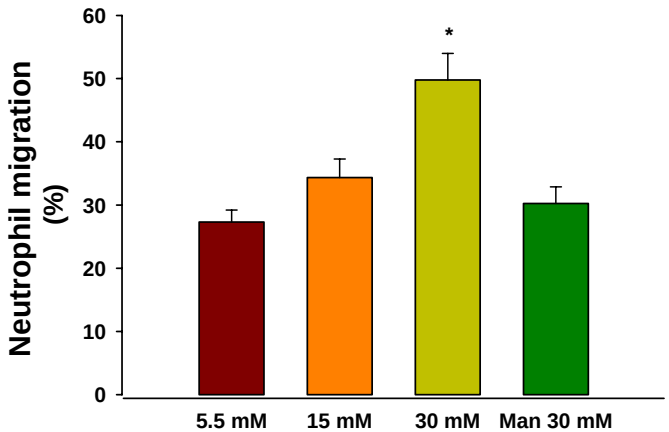
- 대한당뇨병학회지 26권 1호 47 ~ 36, 2002



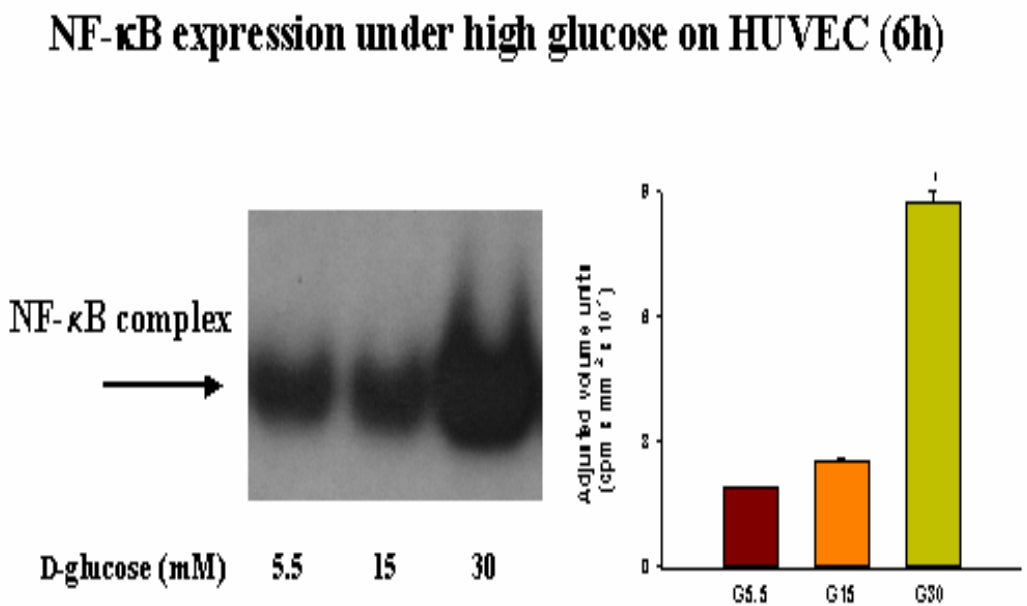
*, P<0.05 vs. 5.5 mM glucose
Man ; Mannitol as osmotic control

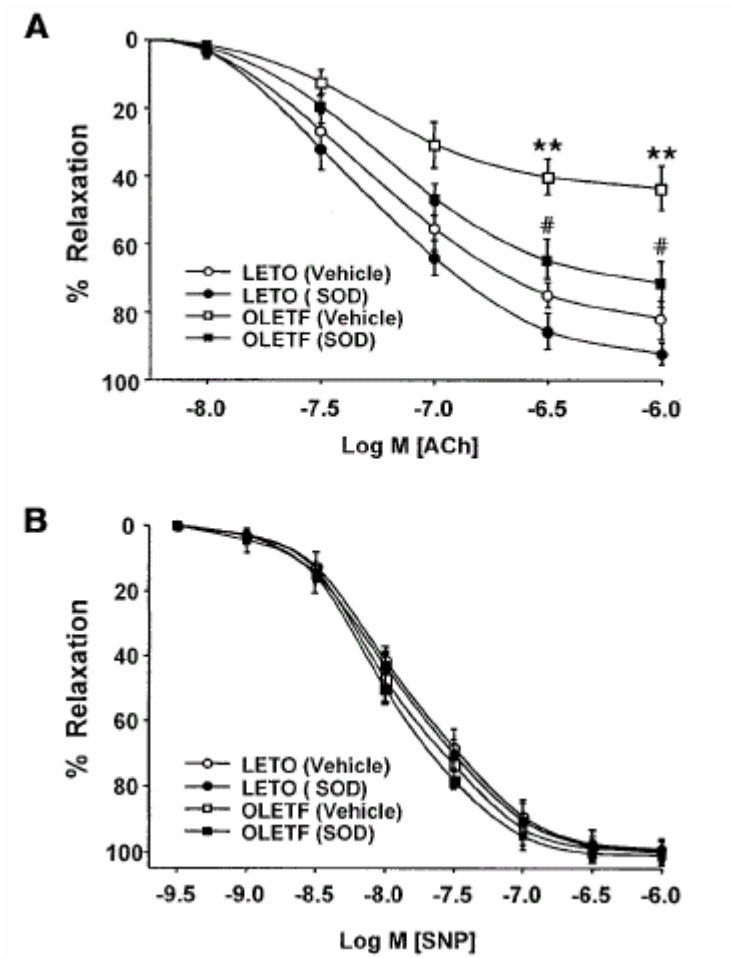


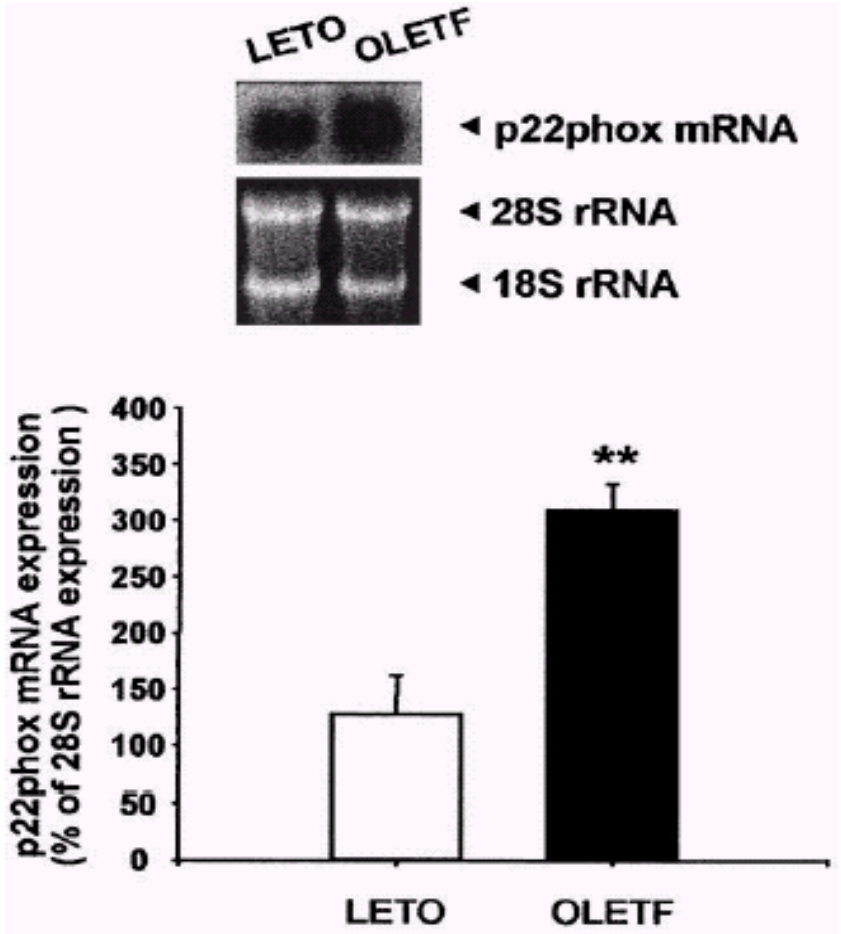
*, P<0.01 vs. 5.5 mM glucose
Man; Mannitol



*, P<0.05 vs. 5.5 mM glucose
Man; Mannitol

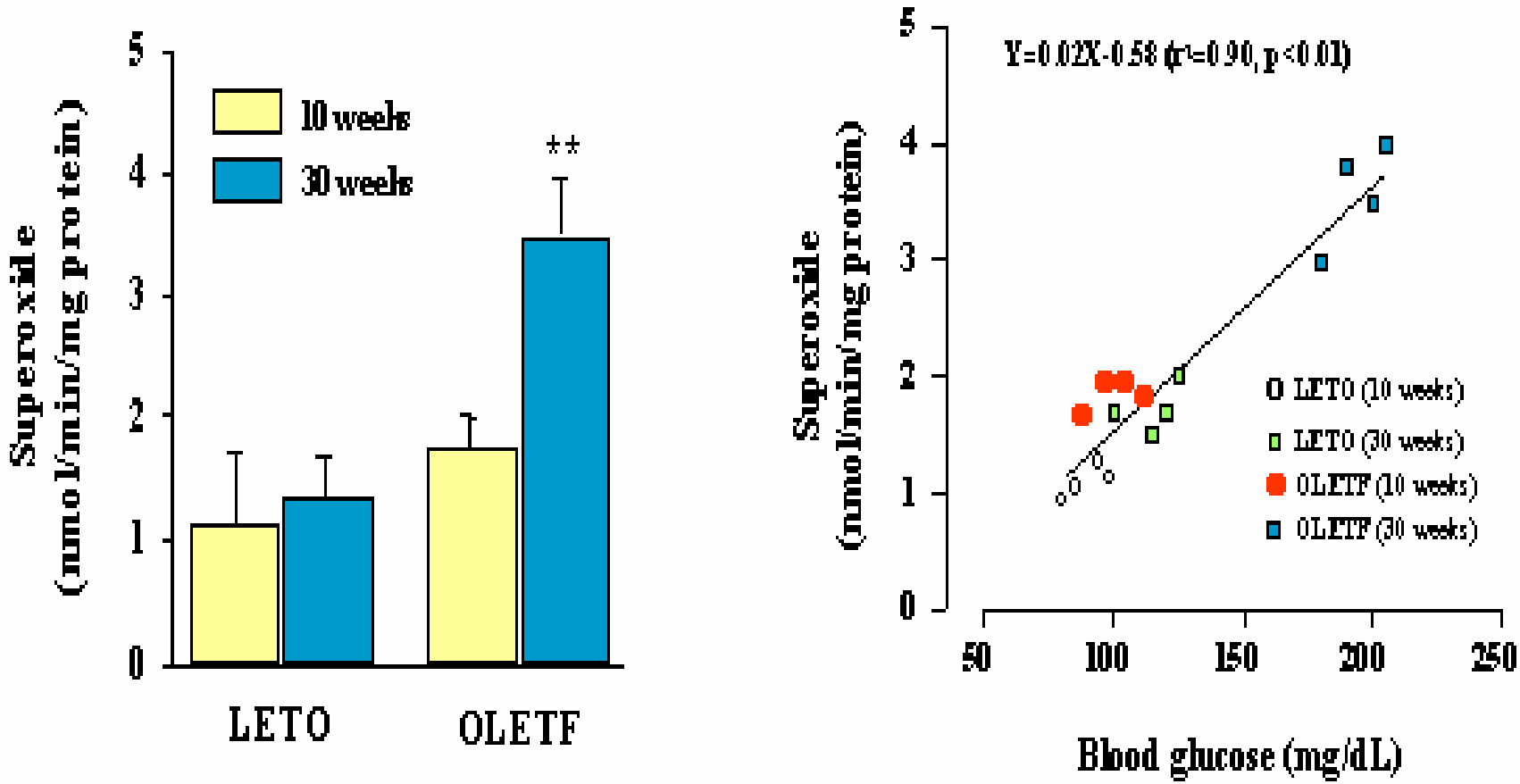






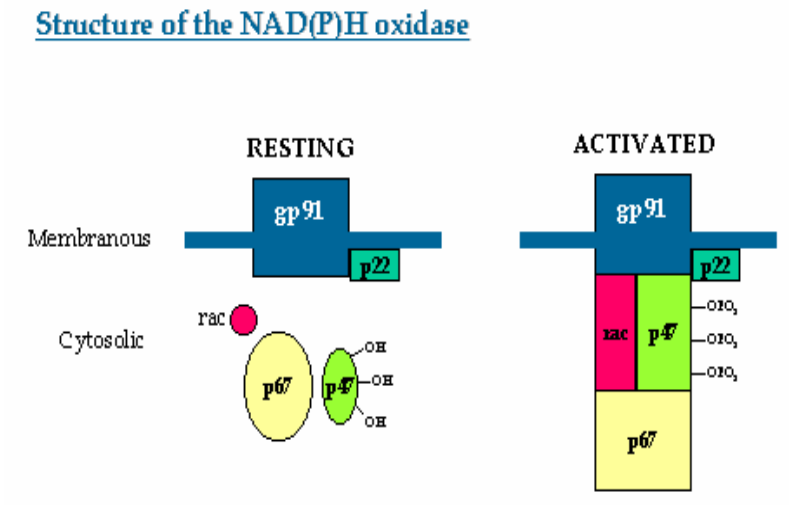
Vascular NADH Oxidase Is Involved in Impaired Endothelium-Dependent Vasodilation in OLETF Rats, a Model of Type 2 Diabetes

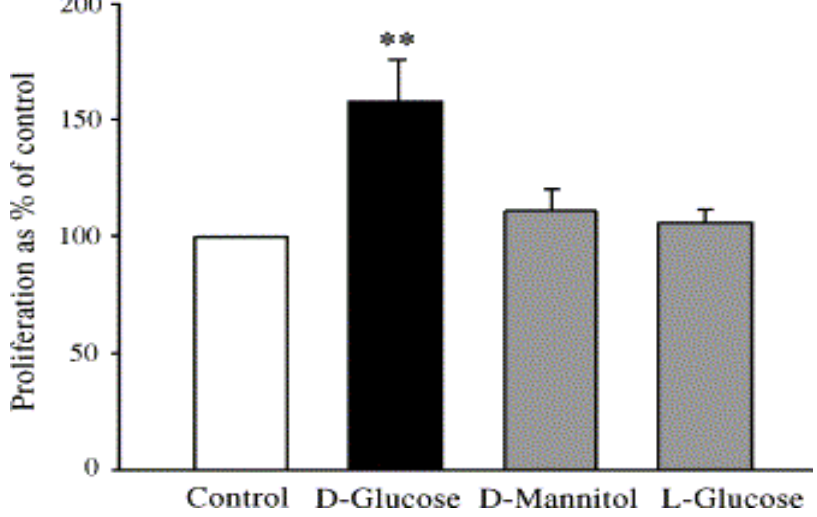
***Diabetes* 51:522–527, 2002**

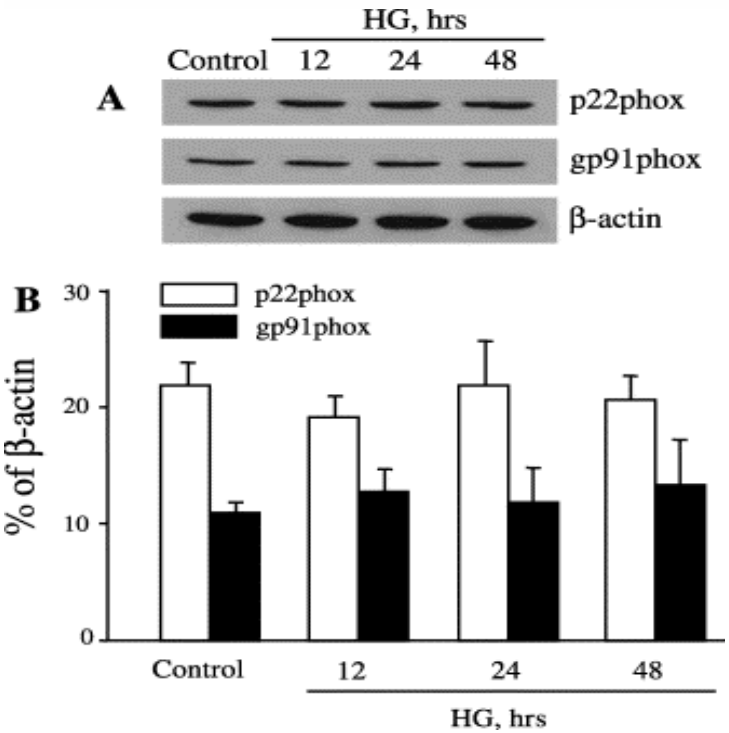


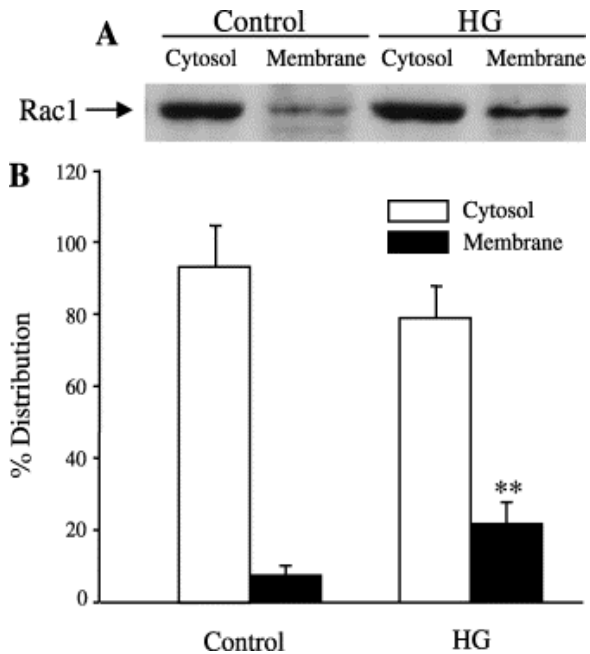
Enhanced vascular production of superoxide in OLETF rat after the onset of hyperglycemia.

Diabetes Research and Clinical Practice 60 (2003) 11 18

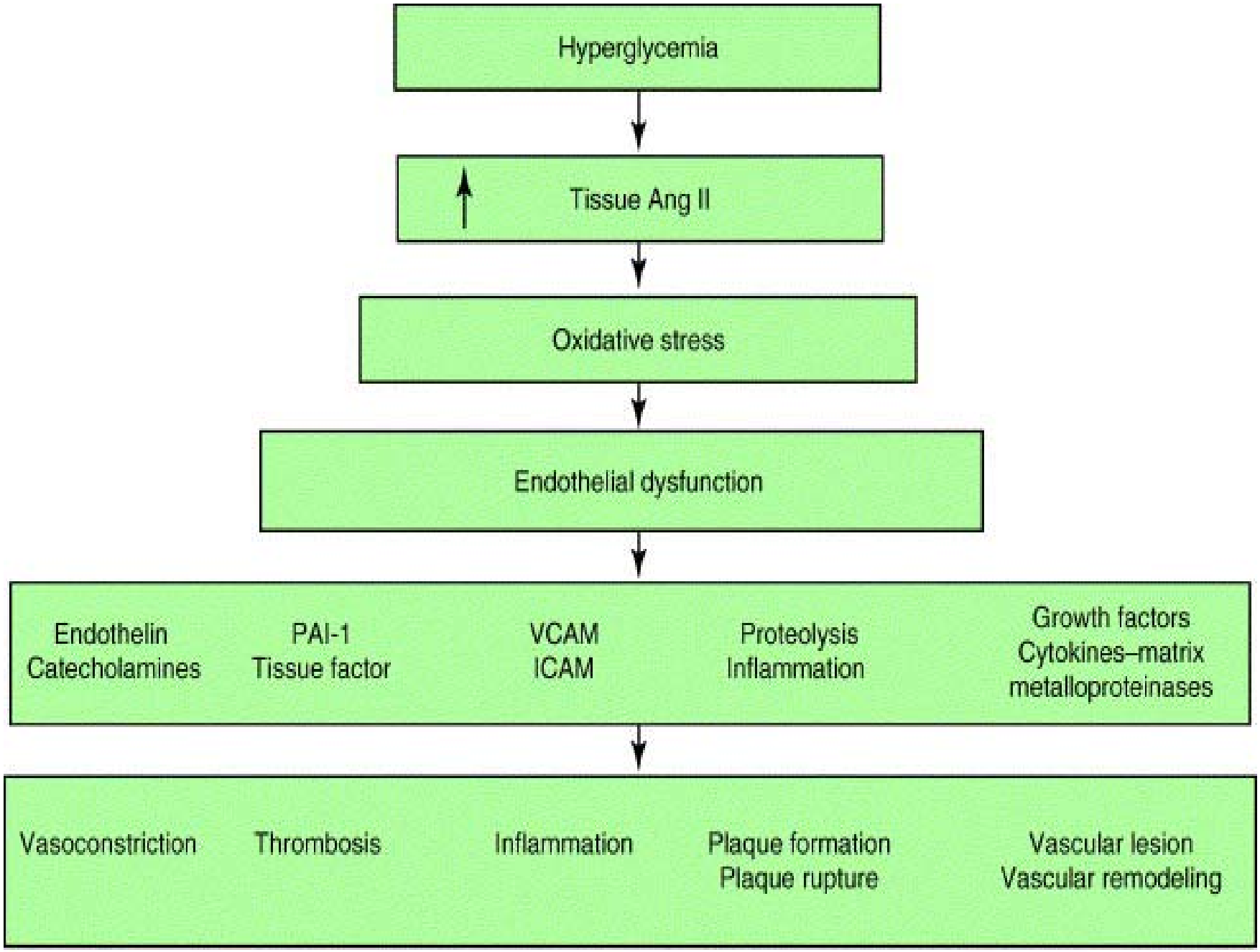




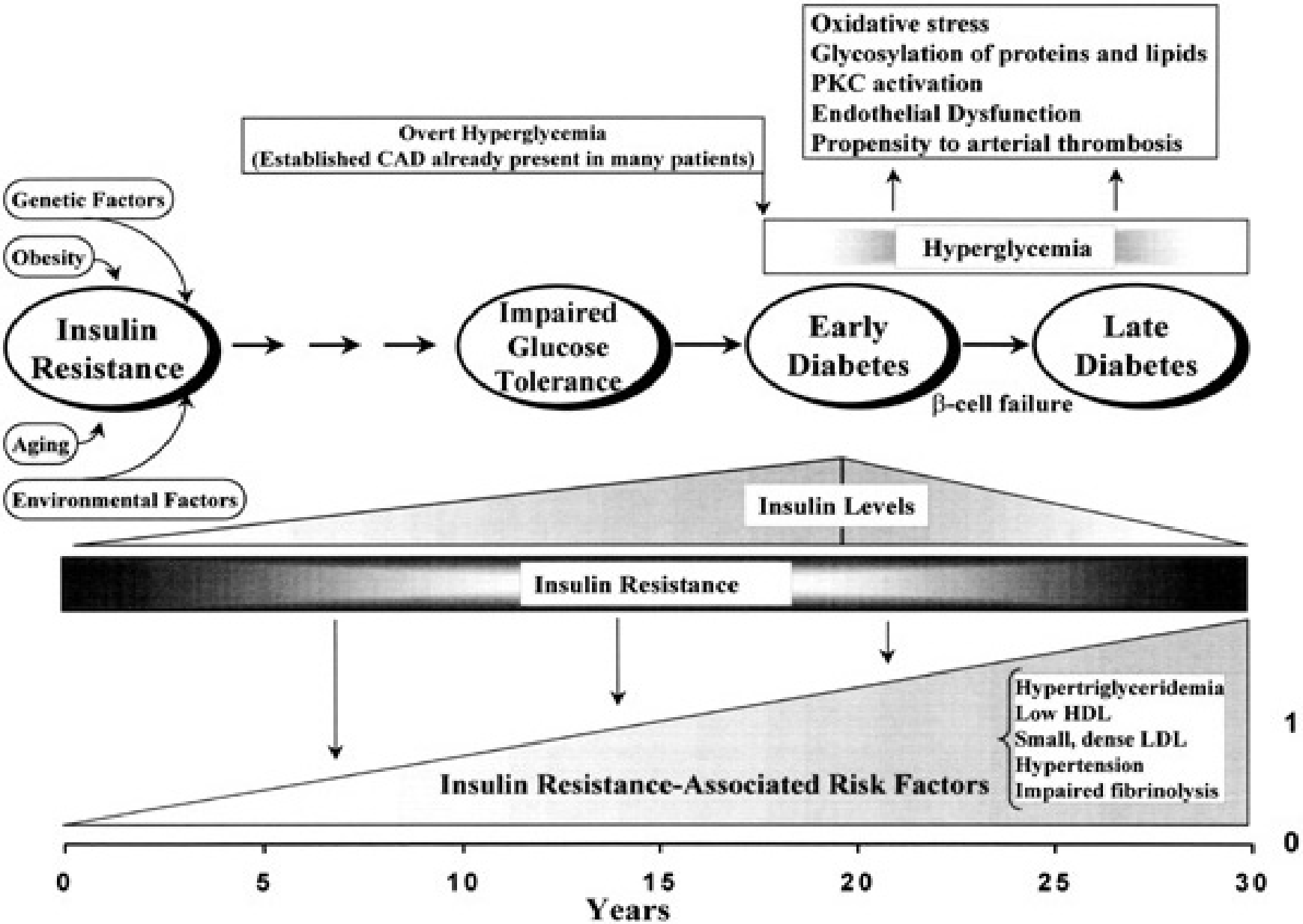




NAD(P)H oxidase participates in the signaling events in high glucose-induced proliferation of vascular smooth muscle cells. Life Sci. 2003 May 2;72(24):2719-30



TRENDS in Endocrinology and Metabolism 2005, 16(3):120-26


Oxidative stress
Glycosylation of proteins and lipids
PKC activation
Endothelial Dysfunction
Propensity to arterial thrombosis
Overt Hyperglycemia
(Established CAD already present in many patients)
Genetic Factors
Obesity
Hyperglycemia
Insulin Resistance
Impaired Glucose Tolerance
Early Diabetes
Late Diabetes
β-cell failure
Aging
Environmental Factors
Insulin Levels
Insulin Resistance
Hypertriglyceridemia
Low HDL
Small, dense LDL
Hypertension
Impaired fibrinolysis
Insulin Resistance-Associated Risk Factors
1
0
0
5
10
15
20
25
30
Years


감사합니다.