Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes and cardiovascular disease? The “Common Soil” hypothesis revisited.

Antonio Ceriello

EASD 2004
From Insulin Resistance to Diabetes

- Reduced Insulin Secretion
- Impaired 1st phase insulin secretion
- Reduced Insulin Secretion
- Cardiovascular Disease
- Microvascular Disease
Perspectives

Microvascular complications of impaired glucose tolerance
Singleton JR et al.

“IGT is also independently associated with traditional microvascular complications of diabetes, including retinopathy, renal disease, and polyneuropathy”

Diabetes 2003
From Insulin Resistance to Diabetes

![Graph showing the progression from Insulin Resistance to Diabetes with indicators for Cardiovascular Disease and Microvascular Disease over a timeline of years.](image-url)
Fat World

We’re Eating More Junk And Getting Less Exercise.

Obesity Is The Globe’s Newest Epidemic.
Glucose
FFA
Cellular Overload

Overnutrition
Decreased Physical Activity
Acetyl-CoA Overload
Overnutrition
Decreased Physical Activity

Glucose
FFA
Cellular Overload

Oxidative Stress
Oxidative Stress

Glucose
FFA
Cellular Overload

Muscle Adipocyte

Overnutrition
Decreased Physical Activity

Oxidative Stress
High glucose level and free fatty acid stimulate reactive oxygen species production through protein kinase C-dependent activation of NAD(P)H oxidase in cultured vascular cells.

Inoguchi T et al.
Ceriello A:  
(insulin resistance associated with oxidative stress)  
*Metabolism* 49: 27-29, 2000

Evans JL et al:  
(oxidative stress induces insulin resistance)  
*Diabetes* 52: 1-8, 2003

Maddux BA et al:  
(FFA induce insulin resistance through oxidative stress)  
*Diabetes* 50: 404-410, 2001

Maechler P et al:  
(glucose induces insulin resistance through oxidative stress)  
*J Biol Chem* 274: 27905-27913, 1999
Glucose Transport is Downregulated by Hyperglycemia in Smooth Muscle Cells

Raber N et al. Diabetes 1999
Overnutrition
Decreased Physical Activity

Glucose FFA Cellular Overload

Muscle Adipocyte
↓ Insulin Resistance

Oxidative Stress
Glucose Transport is Downregulated by Hyperglycemia in Smooth Muscle Cells but not in Endothelial Cells

Raber N et al. Diabetes 1999
High glucose level and free fatty acid stimulate reactive oxygen species production through protein kinase C-dependent activation of NAD(P)H oxidase in cultured vascular cells.

Inoguchi T et al.

Diabetes 2000
Glutathione reverses systemic haemodynamic changes induced by acute hyperglycaemia in healthy subjects

FFA-induced endothelial dysfunction can be corrected by vitamin C.

Pleiner J et al.

*J Clin Endocrinol Metab 2002*
Endothelial cells

Endothelial Dysfunction

Muscle Adipocyte

Insulin Resistance

Oxidative Stress

Glucose

FFA

Cellular Overload

Overnutrition

Decreased Physical Activity
Oxidative Stress

Glucose

FFA

Cellular Overload

Overnutrition

Decreased Physical Activity

Endothelial cells

Endothelial Dysfunction

Muscle

Adipocyte

Insulin Resistance

β cells

Oxidative Stress
Mitochondrial reactive oxygen species reduce insulin secretion by pancreatic beta-cells.

Sakai K et al

BBRC 2003
Oxidative Stress

Overnutrition
Decreased Physical Activity

Glucose
FFA
Cellular Overload

Oxidative Stress

Endothelial cells
↓
Endothelial Dysfunction

Muscle Adipocyte
↓
Insulin Resistance

β cells
↓
Altered Insulin Secretion

Insulin Resistance
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Endothelial Dysfunction

Muscle Adipocyte
Insulin Resistance

β cells
Altered Insulin Secretion

Genetic Predisposition

CVD
Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease

Heitzer T et al.

Patients number: 281  Follow-up: 4.5 years

Conclusion: Endothelial dysfunction and increased oxidative stress predict the risk of cardiovascular events in patients with coronary artery disease. These data support the concept that oxidative stress may contribute not only to endothelial dysfunction, but also to coronary artery disease activity.

Circulation 2001
Oxidative Stress

Glucose

FFA

Cellular Overload

Oxidative Stress

Overnutrition
Decreased Physical Activity

Genetic Predisposition

Endothelial cells
→ Endothelial Dysfunction

Muscle Adipocyte
→ Insulin Resistance

β cells
→ Altered Insulin Secretion

CVD

Metabolic Syndrome

Altered Insulin Secretion

Endothelial Dysfunction

Insulin Resistance

CVD

Metabolic Syndrome
Oxidative Stress

Glucose
FFA
Cellular Overload

Oxidative Stress

Overnutrition
Decreased
Physical Activity

Endothelial cells
Endothelial Dysfunction

Muscle Adipocyte
Insulin Resistance

β cells
Altered Insulin Secretion

IGT (Post Prandial Hyperglycemia)

Genetic Predisposition

CVD

Metabolic Syndrome
Oxidative Stress

Glucose

FFA

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IGT (Post Prandial Hyperglycemia)

CVD

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β cells

Altered Insulin Secretion

IGT (Post Prandial Hyperglycemia)

CVD
The Role of Hyperglycemia and Hypertriglyceridemia in Postprandial Oxidative Stress Generation in Diabetic Patients

Ceriello A et al. Circulation 2002
Oxidative Stress

Overnutrition
- Decreased Physical Activity

Glucose
- FFA
- Cellular Overload

Oxidative Stress

Endothelial cells
- Endothelial Dysfunction

Muscle Adipocyte
- Insulin Resistance

β cells
- Altered Insulin Secretion

IGT (Post Prandial Hyperglycemia)

Diabetes (Chronic Hyperglycemia)

CVD

Metabolic Syndrome

Genetic Predisposition
Oxidative Stress

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CVD
Metabolic Syndrome

Endothelial cells
Endothelial Dysfunction

Muscle Adipocyte
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IGT (Post Prandial Hyperglycemia)
Diabetes (Chronic Hyperglycemia)

Overnutrition
Decreased Physical Activity

Genetic Predisposition

Insulin Resistance
ENDOTHELIAL CELL GLUCOSE UTILIZATION AND GENERATION OF OXIDANTS

Consequences:
- Activation of NF-kB and PKC
- Enhanced intracellular AGE formation
- Sorbitol accumulation

Nature, 2000
Conclusion 1

Evidences suggest that oxidative stress may be the underlying pathogenetic mechanism linking insulin resistance and dysfunction of both beta cells as well as endothelium, which leads to overt diabetes and cardiovascular disease, respectively.
Conclusion 2

Since evidences are cumulating about the possibility of a “specific” and “causal” antioxidant interventions, this hypothesis suggests that oxidative stress may be, in a near future, a therapeutic target to prevent both diabetes and cardiovascular complications.
Prevention of Diabetes Mellitus and Cardiovascular Disease

WOSCOPS: Pravastatin
HOPE: Ramipril
INSIGHT: Nifedipine
LIFE: Losartan
SOLVD: Enalapril
STOP-NIDDM: Acarbose – Post-prandial Hyperglycemia
TRIPOD: Troglitazone

The anti-oxidant effect is the only known property that all of these drugs have in common.
\[ \text{O}_2^- \quad \text{NO}^- \quad \text{OONO}^- \]

- \( \alpha \)-tocopherol
- \( \gamma \)-tocopherol
- Lipid-peroxydes
- Nitrosilation
  - 3-Nitrotyrosine
  - 5-Nitro-\( \gamma \)-tocopherol
Nitrotyrosine  
Risk factor for CVD  
Shishebor MH et al. JAMA 2003

5-Nitro-γ-tocopherol  
Increased in CVD  
**α-tocopherol** with diet

Prevention of CVD

**α-tocopherol**

**γ-tocopherol**

**δ-tocopherol**

Supplementation **α-tocopherol**

No effect on CVD

Reduces the absorption and therefore the plasma levels of **γ-tocopherol**

Huang HY et al J Nutr 2003
Conclusions:

✓ A-tocopherol with diet means increased amounts of g-tocopherol, which can contrast nitrosative stress

✓ A-tocopherol supplementation reduces plasma levels of g-tocopherol, therefore favouring nitrosative stress and may be CVD
Glucose-FFA

\[ \text{ATP} \quad \text{O}_2 \cdot \]
Try one of Our Prime Dry-Aged Meat Packages Today!

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Try one of our All Natural Italian Sauces