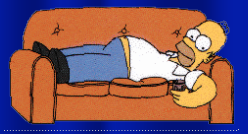
PBF353 mai 2006

Metabolsk syndrom

Definisjon, patofysiologi og cellulære mekanismer



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Metabolsk syndrom
Syndrom X
Insulinresistens syndrom

Forekomst (USA) ≥ 20 år 23.7 %
60- 69 år: 43.5 % !

Økt forekomst av fedme og type 2 diabetes!!

Dødelighet (menn) hjerte-karsykdom x 4.26 (NCEP-ATPIII)
x 2.83 for HKS, 1.77 total dødelighet (WHO)

Metabolsk syndrom og assosierte risikofaktorer for hjerte-karsykdom

Insulin Resistance

- Hypertension
- Abdominal obesity
- Hyperinsulinaemia
- Diabetes
- Hypercoagulability
- Dyslipidaemia
  - high TGs
  - small dense LDL
  - low HDL-C

Atherosclerosis

Endothelial Dysfunction

Metabolsk syndrom
Definisjon WHO 1998

Abdominal fedme
Midje K > 0,85
Hofte M > 0,90
og / eller
BMI > 30 kg/m2

Type 2 DM
Glukosetoleranse ↓
Insulinfølsomhet ↓

Dyslipidemi
Lav HDL
K < 1,0 mmol/L
M < 0,9 mmol/L
og / eller
TG > 1,7 mmol/L

Hypertensjon
> 160 / 90 mmHg

Mikroalbuminuri
> 20 mg/min

Alberti K et al. WHO (1998) Diabetic Medicine 15, 539-553

Metabolsk syndrom 2003

Midjemål
K > 88 cm
M > 102 cm

Fastende glukose > 6,1

Dyslipidemi
Lav HDL
K < 1,3 mmol/L
M < 1,0 mmol/L
og / eller
TG > 1,6 mmol/L

Hypertensjon
≥130 / 85 mmHg
(En eller begge)

National Institute of Health NCEP ATP III, NIH publication 01-3670, August 2003

Metabolsk syndrom (NCEP ATP III)

- Abdominal obesity
- Atherogenic dyslipidemia
- Raised blood pressure
- Insulin resistance ± glucose intolerance
- Proinflammatory state
- Prothrombotic state

Behandling av metabolsk syndrom - velkjent og virksomt!

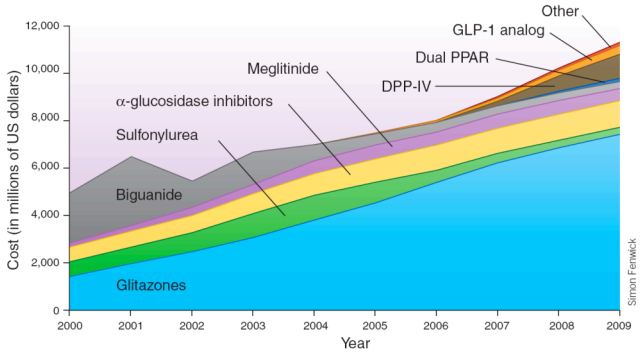
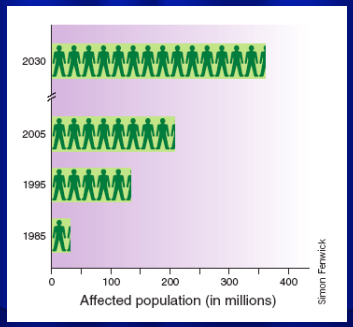
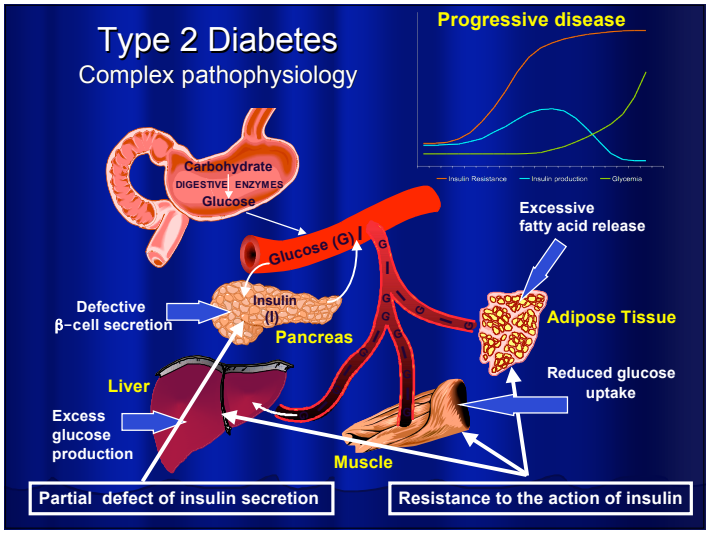


Figure 4 Historical and forecasted growth of the global oral antidiabetic market. Data source: Wood Mackenzie Product view.

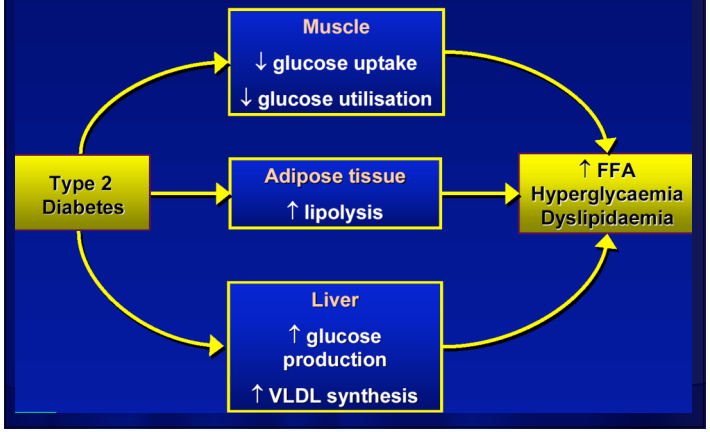
Metabolsk syndrom
Type 2 diabetes



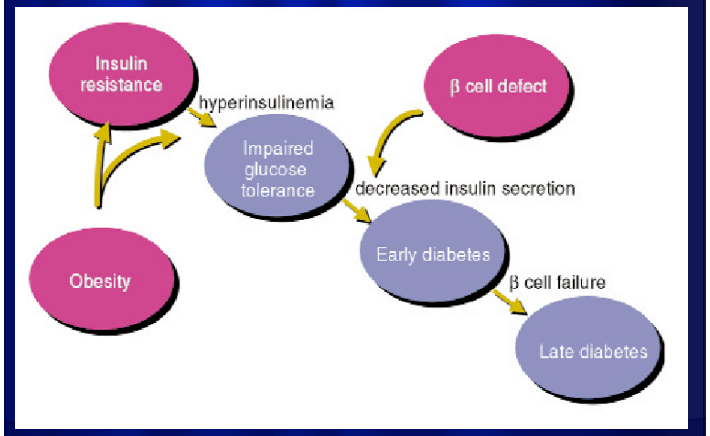
Type 2 Diabetes
Complex pathophysiology



Type 2 Diabetes: Metabolic Imbalance



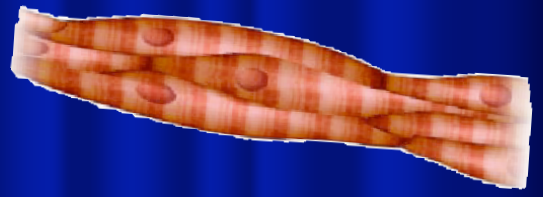
Metabolic staging of type 2 diabetes



Insulinresistens - faktorer av betydning

- Diett
  - Mengde og type fett
  - Sentral fedme (abdominalt fett)
    - Økt frie fettsyrer (og triglyserider)
    - Hypertrofi av fettceller (adipocytter): økt nivå av adipokiner
    - Økt lagring av fett (triglyserider) i muskel og lever (lipotoksisitet - steatose)
  - Hyperglykemi
    - Glukotoksisitet
- Inaktivitet
- Stress
  - Økt kortisol
- Genetikk

Hva skjer i skjelettmuskel?



Cellulære mekanismer?

Insulin resistance in skeletal muscle from patients with Type 2 diabetes is characterized by:

- Impaired insulin-mediated
  - glucose uptake
  - glycogen synthesis
  - glucose oxidation
- Lower lipid oxidation
- Increased intracellular lipid content
- Mitochondrial dysfunction
- Loss of metabolic flexibility

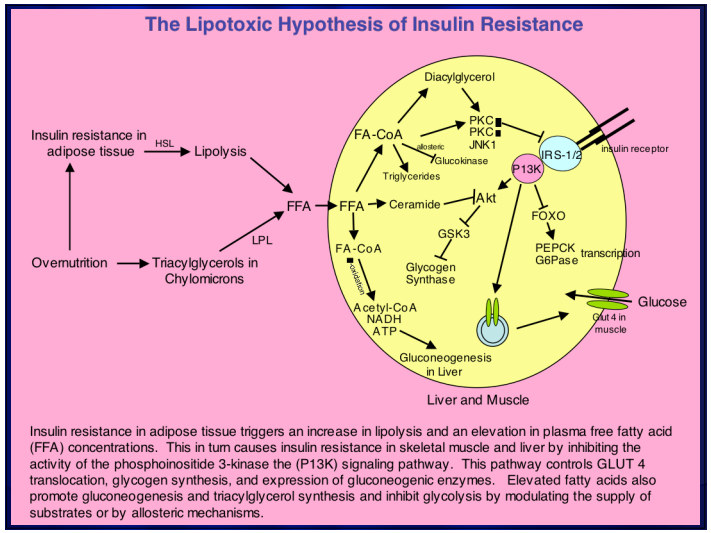
Lipid-induced insulin resistance

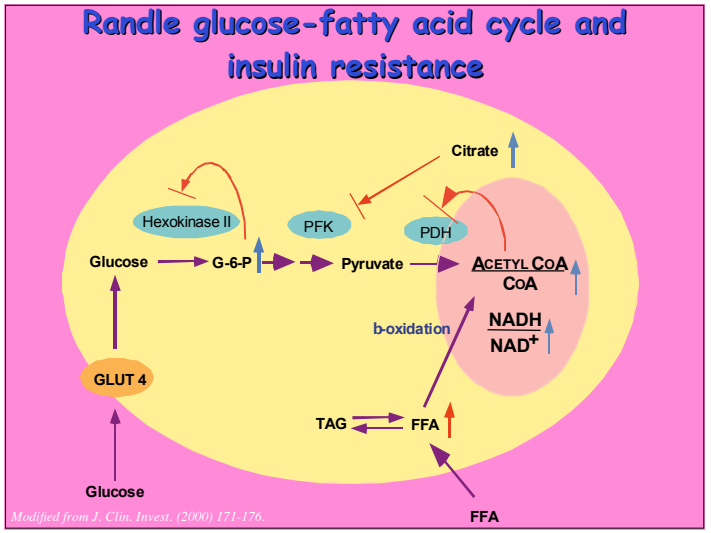
Lipid oversupply:

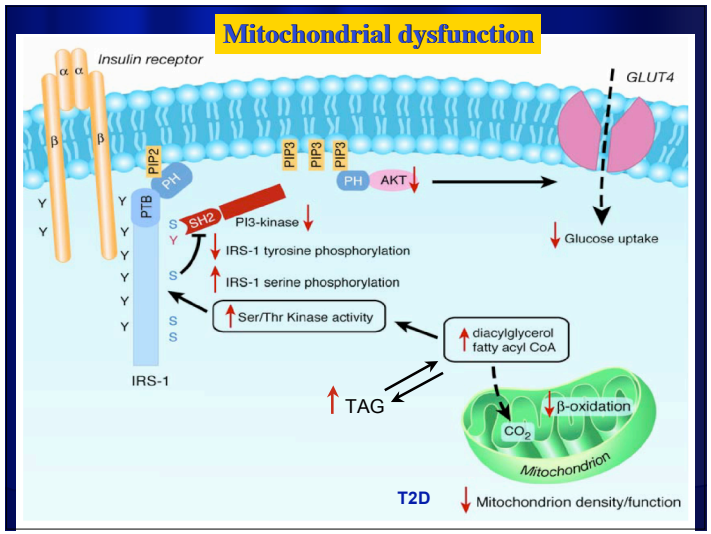
- Change randle glucose-fatty acid cycle
- Alter membrane lipids (composition)
- Promote triacylglycerol (TAG) accumulation
- Increase ceramide biosynthesis
- Increase hexosamine biosynthesis
- Interact with insulin signalling and glucose disposal

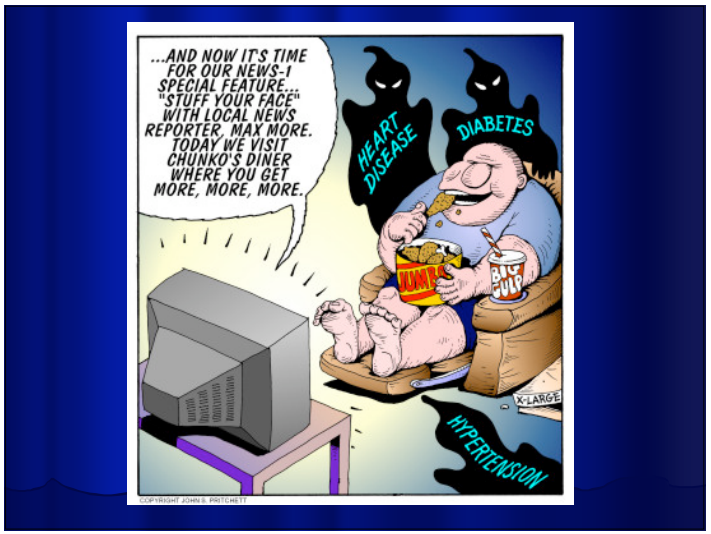
Mitochondrial dysfunction:

- Lipid accumulation and impaired insulin signalling


The Lipotoxic Hypothesis of Insulin Resistance
Insulin resistance in adipose tissue
HSL
Lipolysis
FFA
Overnutrition
Triacylglycerols in Chylomicrons
LPL
Diacylglycerol
FA-CoA
PKC
PKC
JNK1
allosteric
Glucokinase
Triglycerides
IRS-1/2
insulin receptor
P13K
FFA
Ceramide
Akt
FOXO
GSK3
FA-CoA
oxidation
Glycogen Synthase
PEPCK G6Pase
transcription
Acetyl-CoA
NADH
ATP
Gluconeogenesis in Liver
Glucose
Glut 4 in muscle
Liver and Muscle
Insulin resistance in adipose tissue triggers an increase in lipolysis and an elevation in plasma free fatty acid (FFA) concentrations. This in turn causes insulin resistance in skeletal muscle and liver by inhibiting the activity of the phosphoinositide 3-kinase the (P13K) signaling pathway. This pathway controls GLUT 4 translocation, glycogen synthesis, and expression of gluconeogenic enzymes. Elevated fatty acids also promote gluconeogenesis and triacylglycerol synthesis and inhibit glycolysis by modulating the supply of substrates or by allosteric mechanisms.


Randle glucose-fatty acid cycle and insulin resistance
Citrate
Hexokinase II
PFK
PDH
Glucose
G-6-P
Pyruvate
ACETYL CoA
CoA
b-oxidation
NADH
NAD+
GLUT 4
TAG
FFA
Glucose
FFA
Modified from J. Clin. Invest. (2000) 171-176.


Mitochondrial dysfunction
Insulin receptor
GLUT4
PIP2
PIP3
PH
AKT
PTB
SH2
PI3-kinase
IRS-1 tyrosine phosphorylation
IRS-1 serine phosphorylation
Ser/Thr Kinase activity
diacylglycerol
fatty acyl CoA
IRS-1
TAG
β-oxidation
CO2
Mitochondrion
T2D
Mitochondrion density/function
Glucose uptake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