Mitochondrial genetics and metabolic syndrome in postmenopausal women

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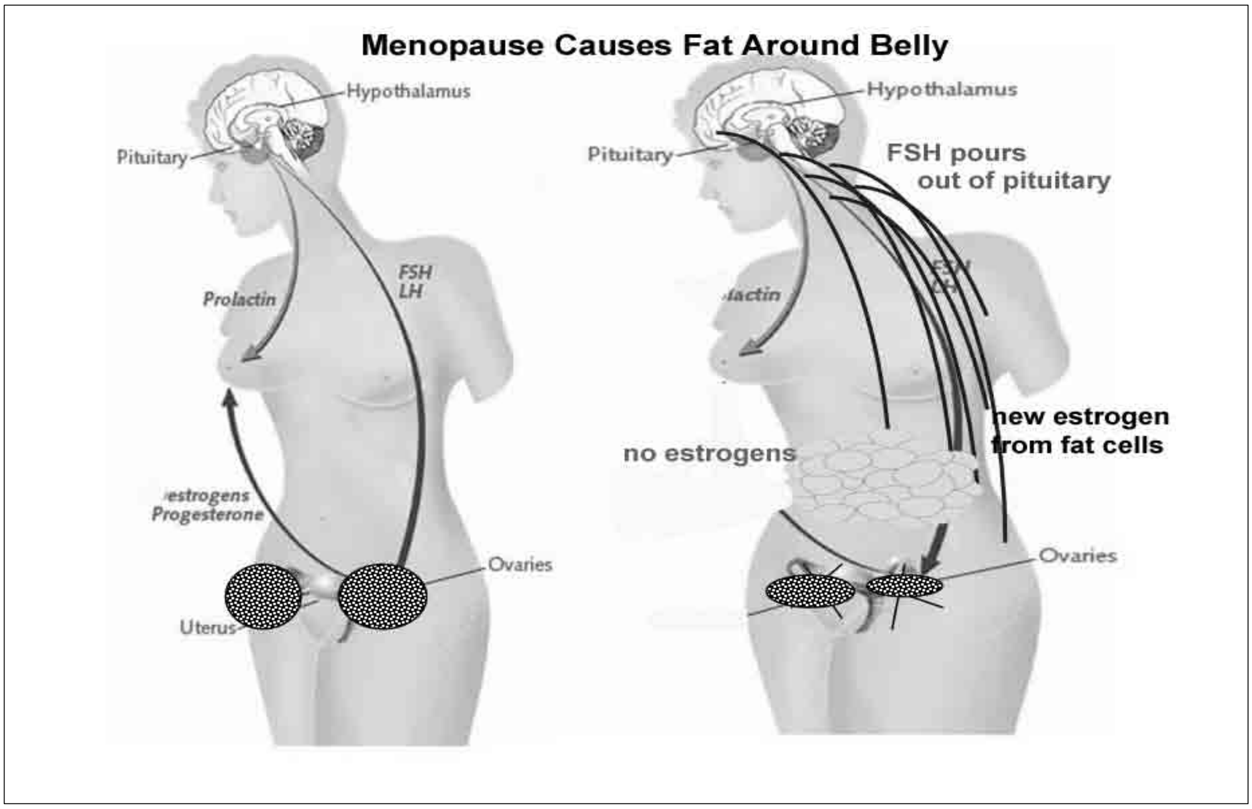
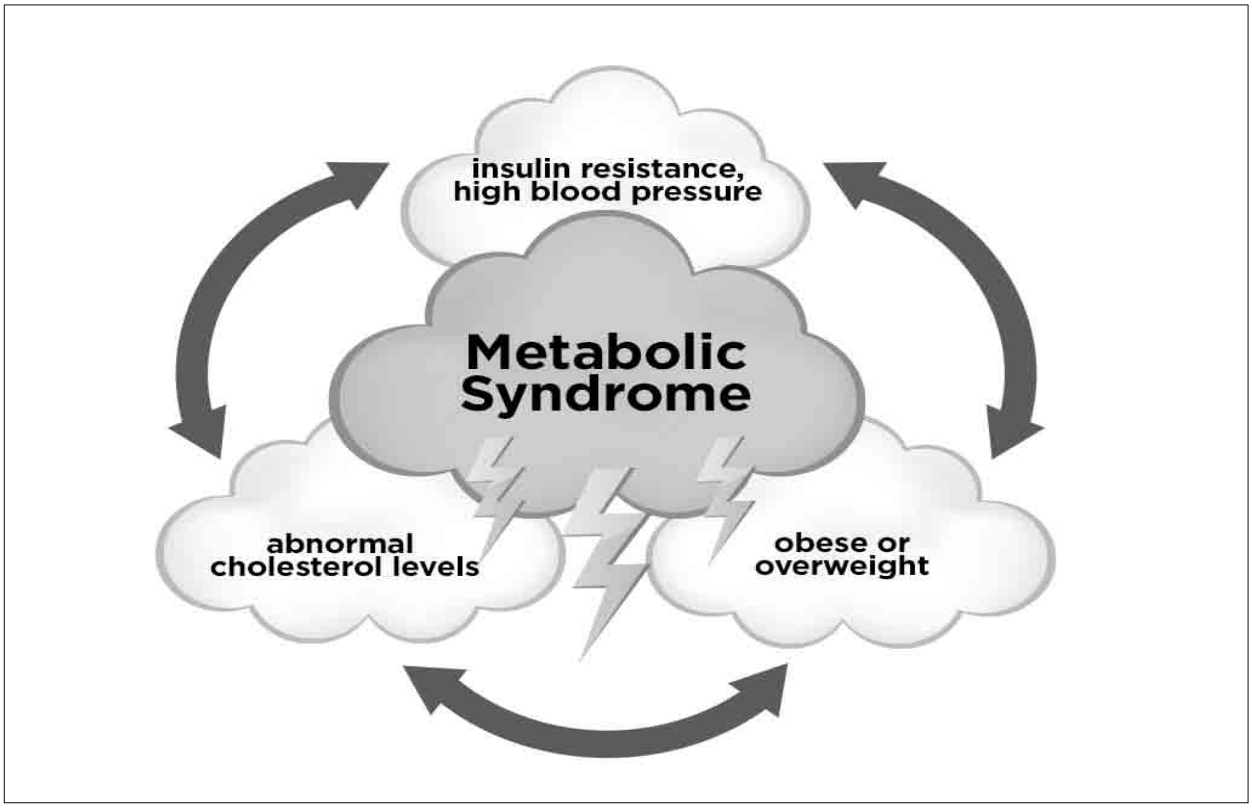
Menopause and metabolic syndrome


Menopause Causes Fat Around Belly
Hypothalamus
Pituitary
Prolactin
FSH
LH
estrogens
Progesterone
Ovaries
Uterus
Hypothalamus
Pituitary
FSH pours
out of pituitary
new estrogen
from fat cells
no estrogens
Ovaries

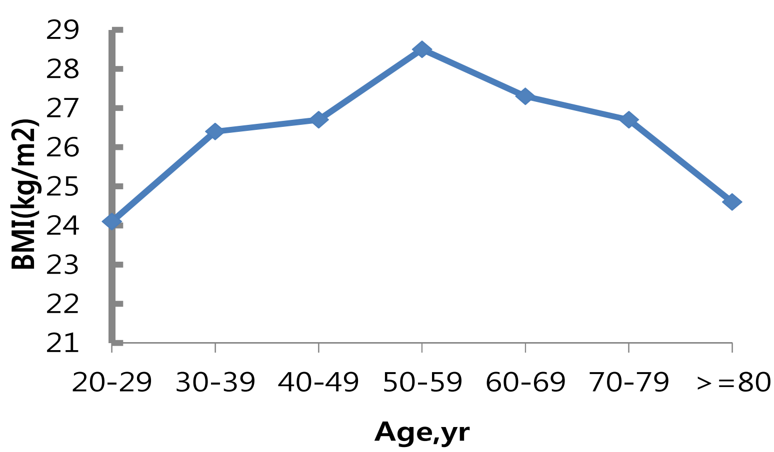

insulin resistance,
high blood pressure
Metabolic
Syndrome
abnormal
cholesterol levels
obese or
overweight

Metabolic syndrome in post menopausal women (NACEP ATP III)

- Hypertension
  - BP ≥ 130 or 85 mmHg
- *Abdominal obesity*
  - WC >80cm
- Dyslipidemia
  - HDL-C <50mg/dL
  - TG ≥150mg/dL
- Insulin resistance
  - AC ≥ 100mg/dL

3 or more above criteria

Weight Change with Aging for Women



JAMA 272:208, 1994.

Menopause and Metabolic syndrome

2.5 kg weight gain over 3 years during the menopausal transition

Menopause 60% increased risk of MetS

In SWAN, prevalence of MetS
- 32.6% before FMP
- 13.7% newly developed in FMP

progressively increased incidence of MetS after 6 years following FMP

Curr Opin Obstet Gynecol 2012, 24:402-407

Comorbidities associated with postmenopausal MetS

CVD	RR 2.24
CHD	RR 1.54
T2DM	6-7 folds up

Higher frequency of
- hot flashes
- night sweats
- higher score MRS

Curr Opin Obstet Gynecol 2012, 24:402–407

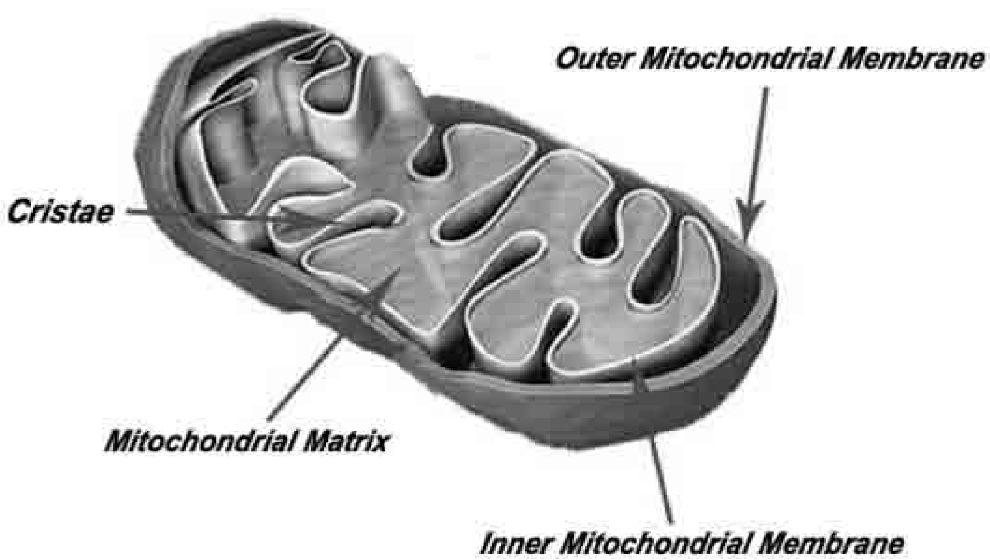
Association of Menopause and MetS

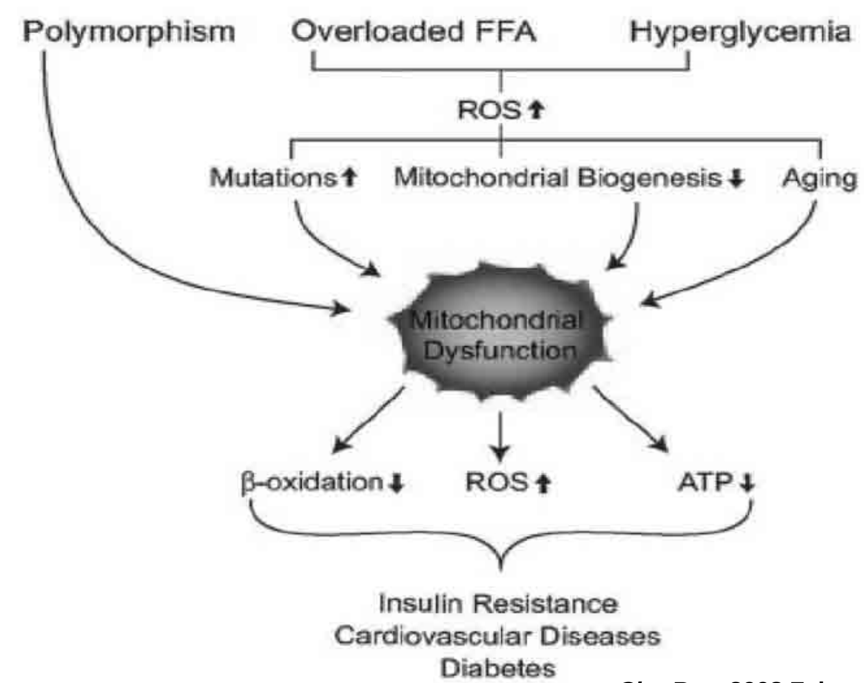
Menopause is an independent risk factor for MetS after adjusting confounding factors (age, BMI, income, physical activity)

→ Estrogen may have a protective role against MetS.

And then what is the underlying mechanism??

The Mitochondrion





Circ Res. 2008 February 29; 102(4): 401–414

Estrogen exerts pivotal role for mitochondrial function and biogenesis

Direct

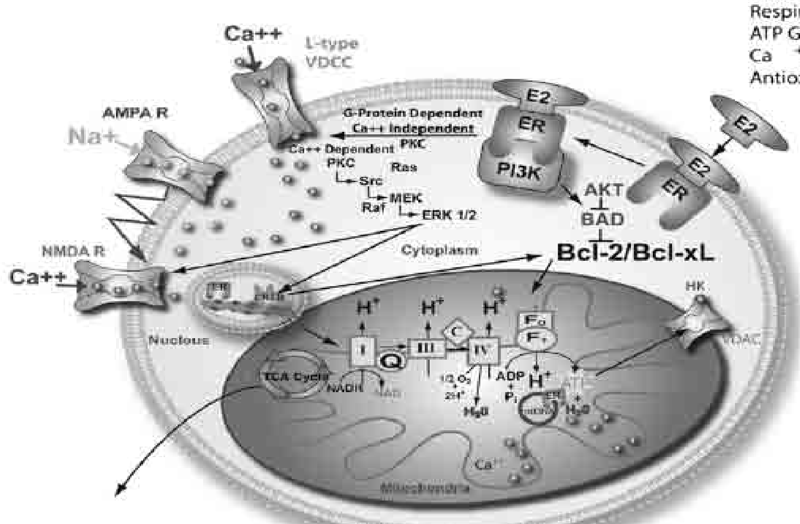
- Stabilization of the $\Delta\psi m$
- Inhibition of FOF1-AYPase
- Augment mitochondrial seqeustration of Ca^{+2}
- Direct antioxidant effects

Indirect

- increased nuclear transcription
- increased mitochondrial transcription
- Activation of intracellular signaling protein

Estrogen mechanisms of action converge upon the mitochondria.

Increased:
Aerobic Glycolysis
Respiratory Efficiency
ATP Generation
Ca Load Tolerance
Antioxidant Defense



Increased oxphos-coupled glycolysis
Prevent use of alternative energy source
Prevent mitochondrial dysfunction
Prevent Alzheimer's bioenergetic phenotype

Advances in Pharmacology, 2012;64:327

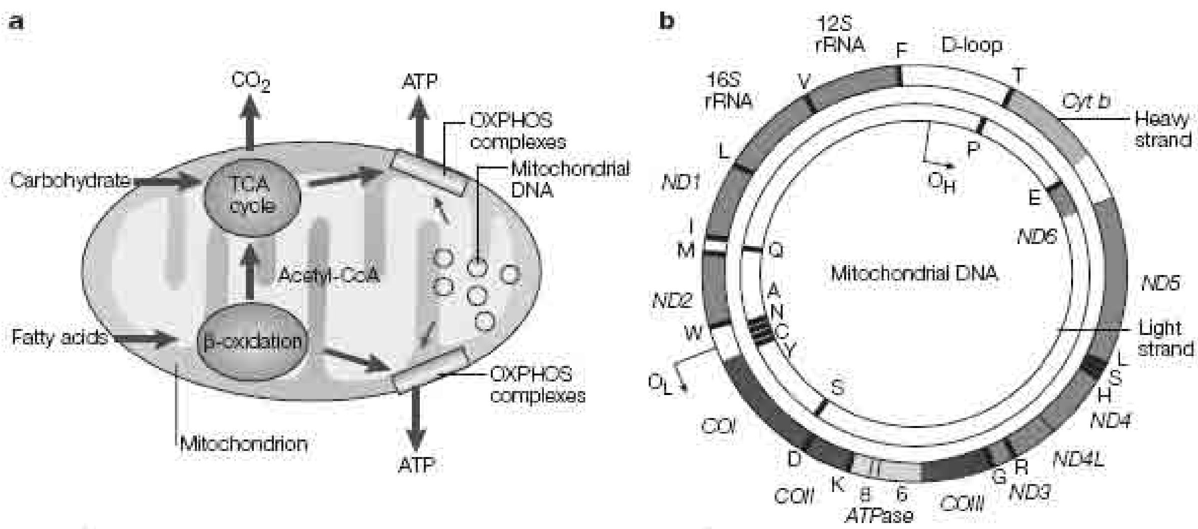
Estrogen deficiency may contribute

→ decreased mitochondrial function and biogenesis

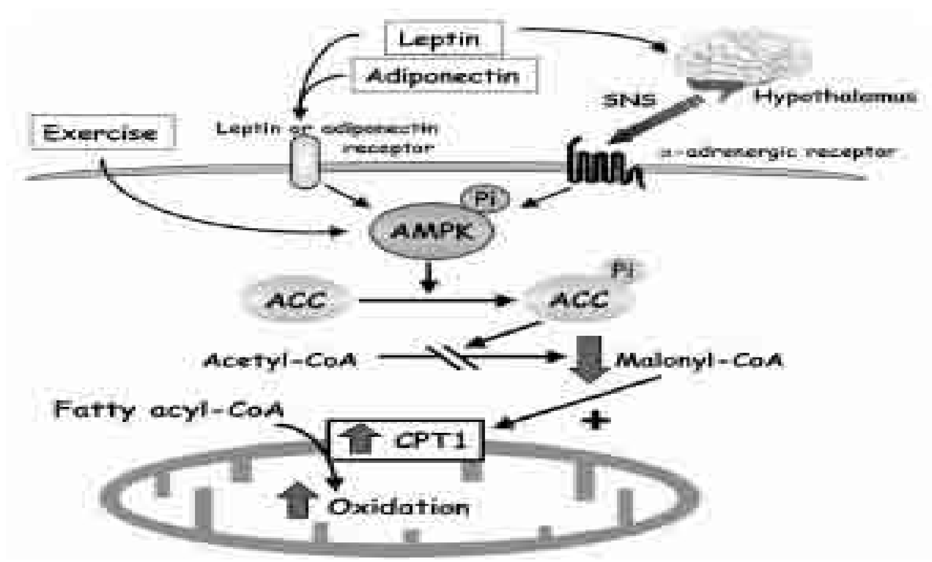
→ increasing prevalence of MetS in postmenopausal women

?

Mitochondrial 기능과 DNA 구조

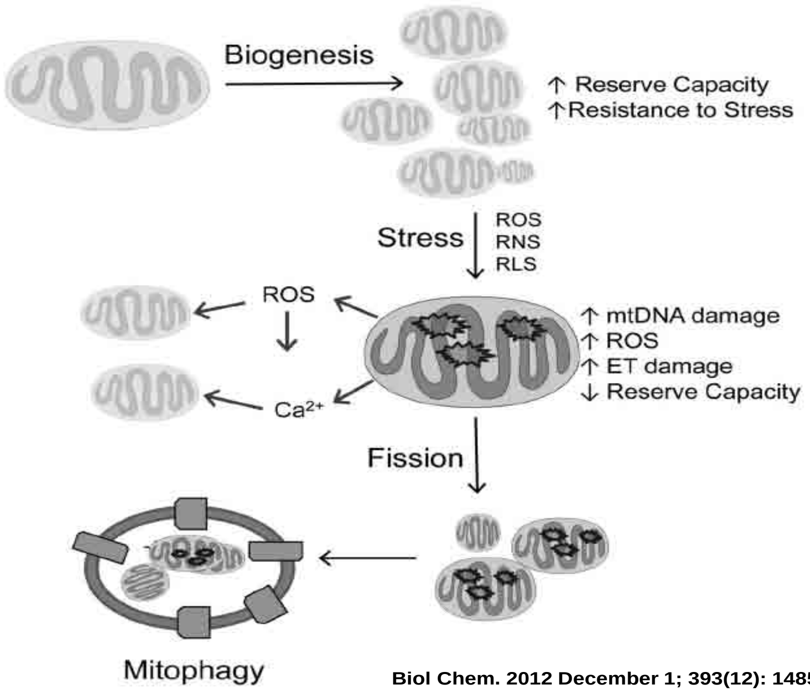


Central regulation of energy metabolism via AMPK and mitochondria



Khan BB et al. Cell metabolism 2005:1:15-25

Regulation of mitochondrial quality control and the response to oxidative stress



Biol Chem. 2012 December 1; 393(12): 1485–1512

Mitochondria dysfunction and human disease

- Aging process
- CVD and/or CHF
- Diabetes
- Obesity and metabolic syndrome
- Neurodegenerative disease
    - Parkinson disease
    - Alzheimer disease
- Cancer
- Neuroimmunomodulation

1. Mitochondria and Obesity

Genes correlated with BMI and metabolic syndrome

- To identify obesity related gene expression in agouti mice
- 1304 transcripts were significantly correlated with BMI
- Analysis of 100 most significant transcript
  - 30% encoded protein characteristically expressed by macrophage
  - 6% encoded lysosomal proteins
  - 12% encoded mitochondrial protein

key pathophysiologic process for Obesity??

1. Deficient in ATP production →→ inadequate energy supply →→ Increased appetite.

2. Reduction of mitochondrial area and abundance

Mitochondrial dysfunction

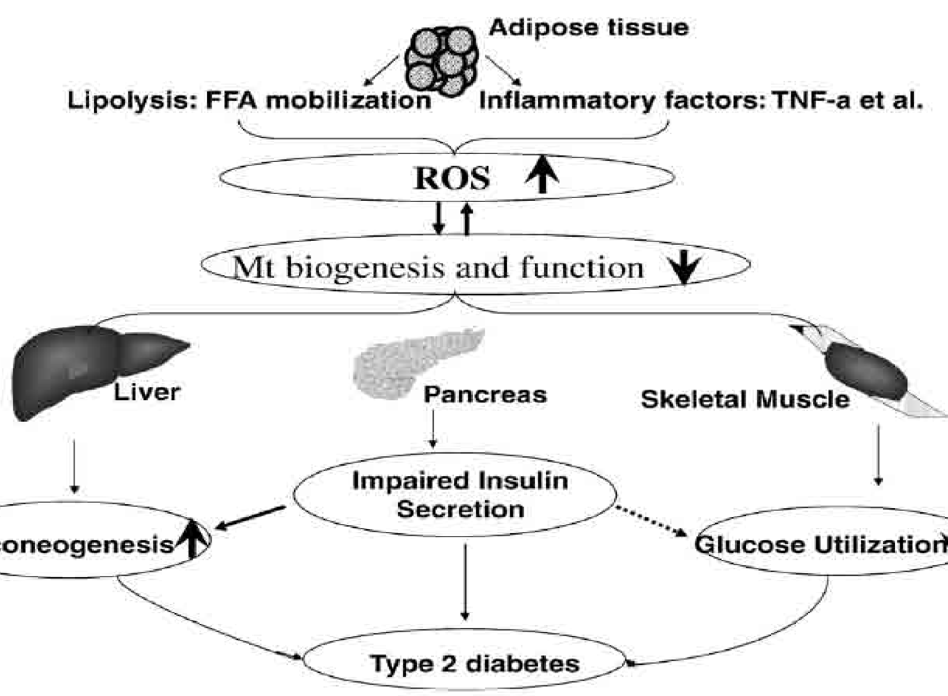
Mitochondrial biogenesis in impaired in obesity

In 3 obese mice model (ob/ob, fa/fa, DIO) mitochondrial biogenesis was found to be markedly decrease

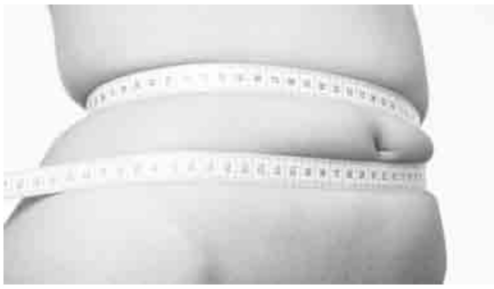
- mitochondrial biogenesis
  - PGC-1 α
  - NRF-1
  - mtDNA transcription factor A (Tfam)
  - mtDNA
- mitochondrial function
  - Respiratory protein (COX IV, Cyt c)
  - Oxygen consumption and ATP production

2. Mitochondria and Type 2 DM

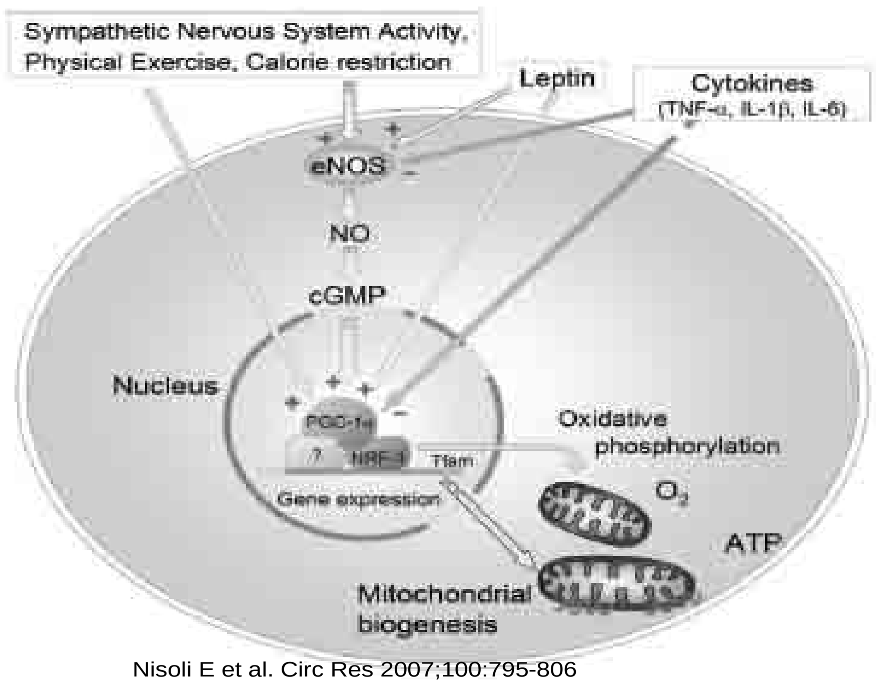
J. Liu et al. / Advanced Drug Delivery Reviews 61 (2009) 1343–1352



3. Mitochondria and MetS in postmenopausal women ??



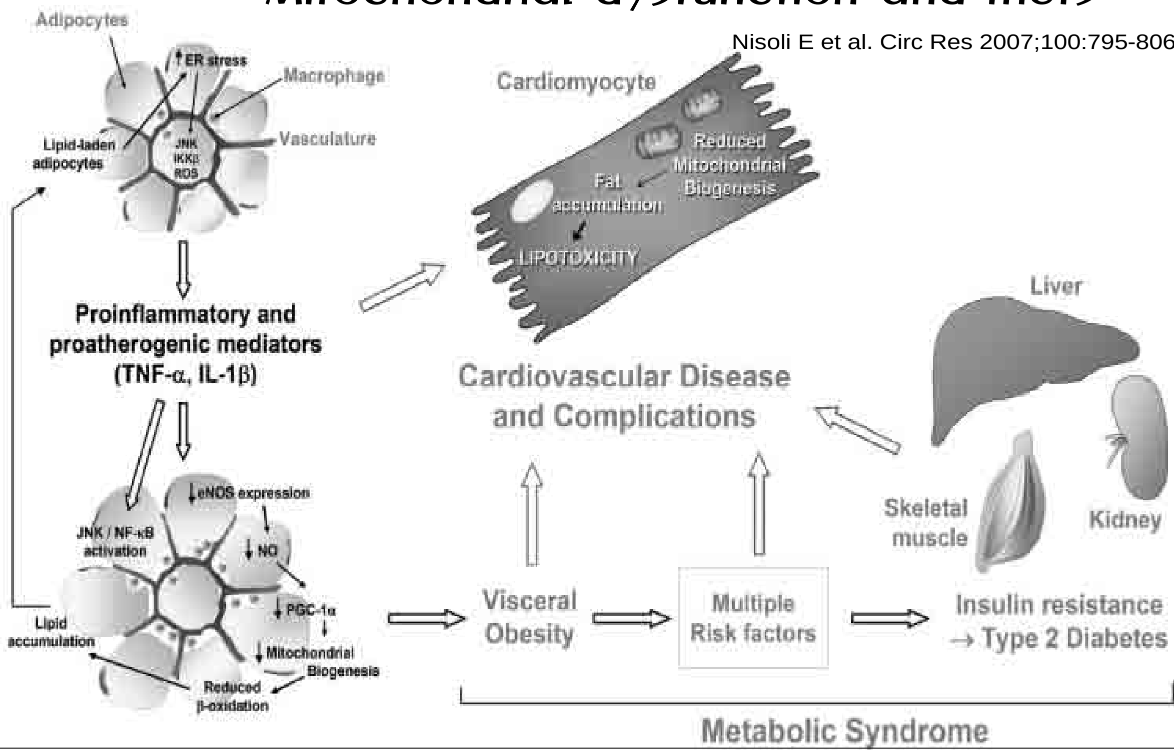
Mitochondrial biogenesis

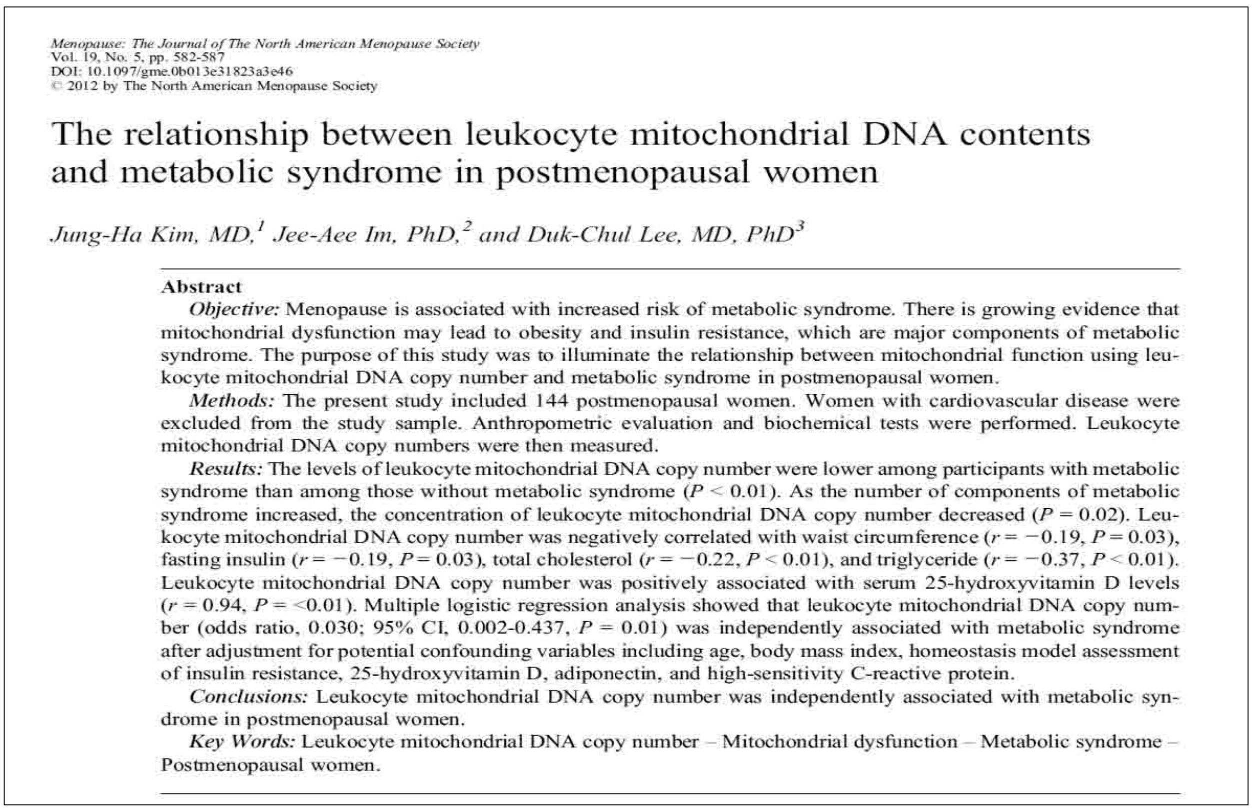


Nisoli E et al. Circ Res 2007;100:795-806

Mitochondrial dysfunction and metS

Nisoli E et al. Circ Res 2007;100:795-806





Menopause: The Journal of The North American Menopause Society
Vol. 19, No. 5, pp. 582-587
DOI: 10.1097/gme.0b013e31823a3e46

The relationship between leukocyte mitochondrial DNA contents and metabolic syndrome in postmenopausal women

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Abstract

Objective: Menopause is associated with increased risk of metabolic syndrome. There is growing evidence that mitochondrial dysfunction may lead to obesity and insulin resistance, which are major components of metabolic syndrome. The purpose of this study was to illuminate the relationship between mitochondrial function using leukocyte mitochondrial DNA copy number and metabolic syndrome in postmenopausal women.

Methods: The present study included 144 postmenopausal women. Women with cardiovascular disease were excluded from the study sample. Anthropometric evaluation and biochemical tests were performed. Leukocyte mitochondrial DNA copy numbers were then measured.

Results: The levels of leukocyte mitochondrial DNA copy number were lower among participants with metabolic syndrome than among those without metabolic syndrome ($P < 0.01$). As the number of components of metabolic syndrome increased, the concentration of leukocyte mitochondrial DNA copy number decreased ($P = 0.02$). Leukocyte mitochondrial DNA copy number was negatively correlated with waist circumference ($r = -0.19$, $P = 0.03$), fasting insulin ($r = -0.19$, $P = 0.03$), total cholesterol ($r = -0.22$, $P < 0.01$), and triglyceride ($r = -0.37$, $P < 0.01$). Leukocyte mitochondrial DNA copy number was positively associated with serum 25-hydroxyvitamin D levels ($r = 0.94$, $P = <0.01$). Multiple logistic regression analysis showed that leukocyte mitochondrial DNA copy number (odds ratio, 0.030; 95% CI, 0.002-0.437, $P = 0.01$) was independently associated with metabolic syndrome after adjustment for potential confounding variables including age, body mass index, homeostasis model assessment of insulin resistance, 25-hydroxyvitamin D, adiponectin, and high-sensitivity C-reactive protein.

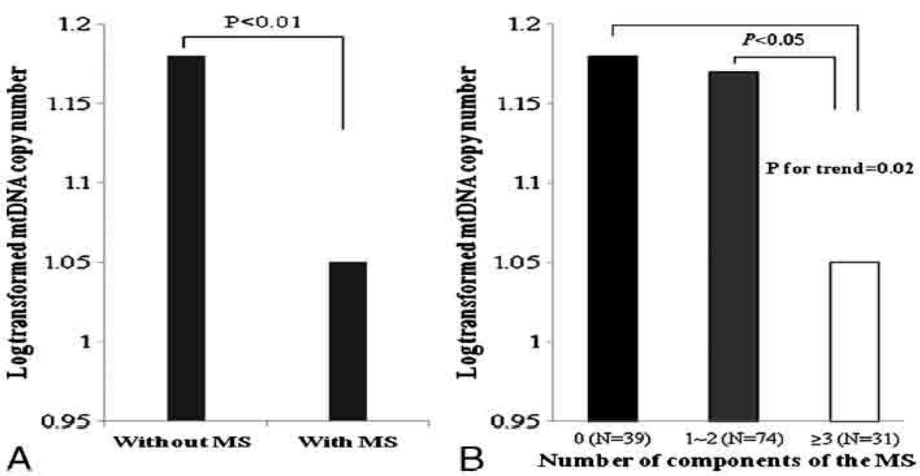
Conclusions: Leukocyte mitochondrial DNA copy number was independently associated with metabolic syndrome in postmenopausal women.

Key Words: Leukocyte mitochondrial DNA copy number – Mitochondrial dysfunction – Metabolic syndrome – Postmenopausal women.

TABLE 3. *Correlation between leukocyte mitochondrial DNA copy number and various metabolic parameters*

Variables	*r*	*P*
Age	0.08	0.35
Body mass index	−0.06	0.48
Waist circumference	−0.19	0.03
Systolic blood pressure	−0.04	0.63
Diastolic blood pressure	−0.10	0.24
Fasting glucose	−0.02	0.83
Fasting insulin	−0.19	0.03
HOMA-IR	−0.15	0.07
Total cholesterol	−0.22	<0.01
Triglycerides[a]	−0.37	<0.01
HDL-cholesterol	0.09	0.26
LDL-cholesterol	−0.04	0.61
hs-CRP	0.09	0.26
Homocysteine	−0.08	0.37
Adiponectin[a]	0.14	0.08
25-Hydroxyvitamin D[a]	0.94	<0.01
Uric acid	0.07	0.42

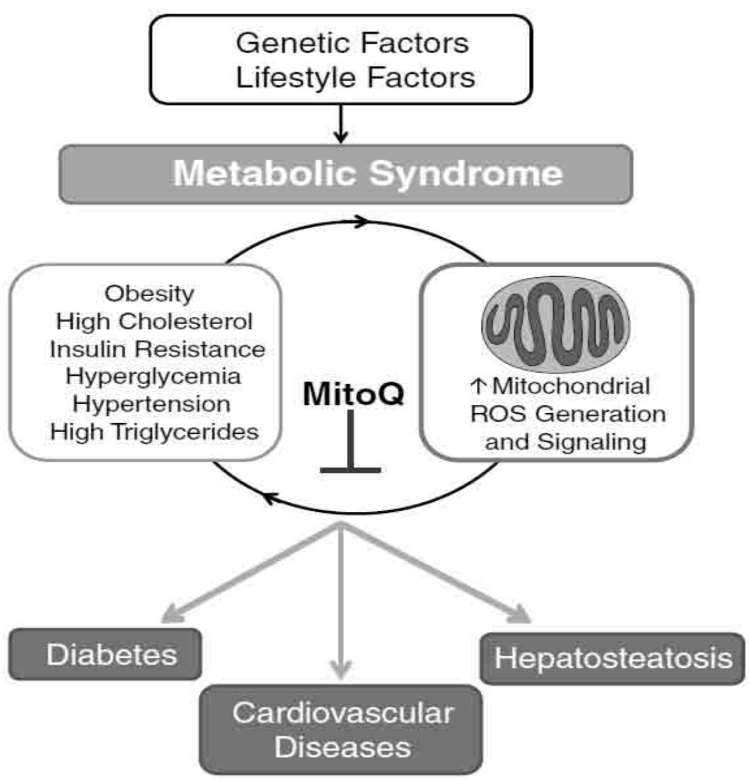
Mitochondrial DNA contents and MetS in postmenopausal women



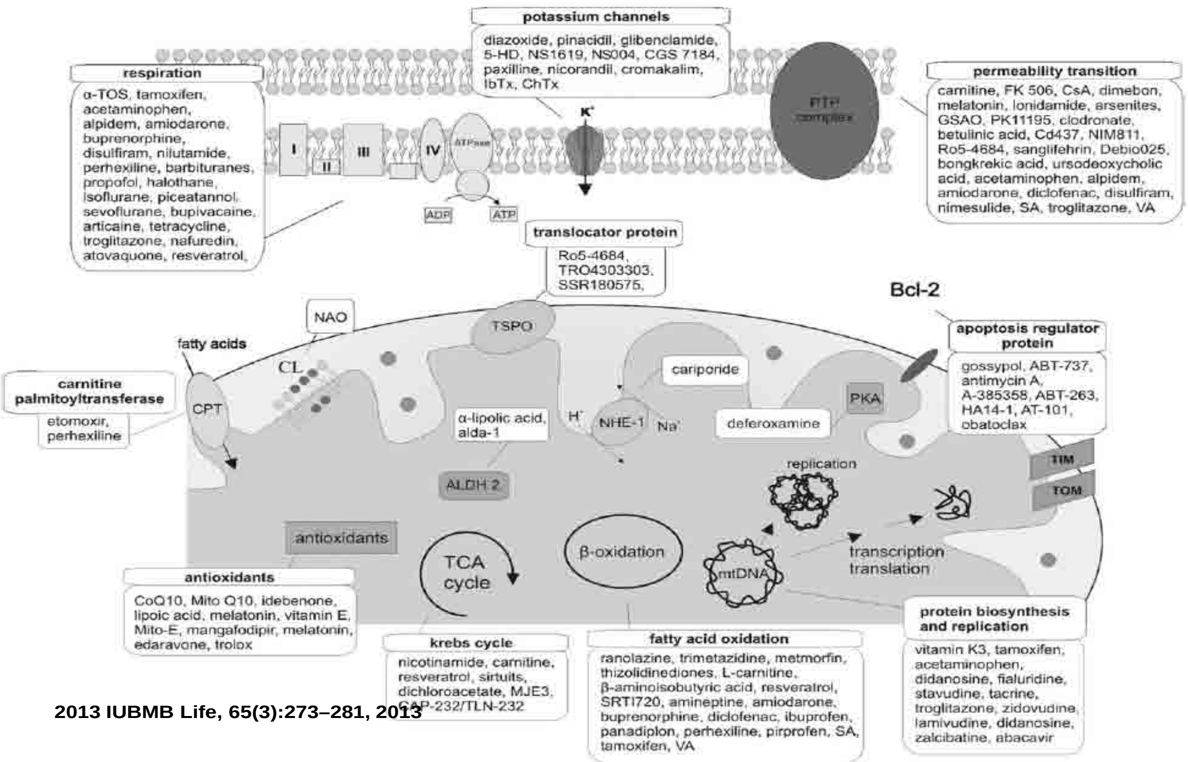
Menopause, 2012;19(5),:582-587

Mitochondrial biogenesis

- ✓ Regular exercise
- ✓ Caloric restriction
- ✓ SIRTUIN – SIRT1, SIRT3
- ✓ AMPK activator
- ✓ Mitochondrial targeted antioxidants – MitoQ etc



Free Radical Biology & Medicine 52 (2012) 838-840



2013 IUBMB Life, 65(3):273–281, 2013

Summary and future direction

- ✓ In obesity and/or Type 2 DM patients, mitochondrial energy production and biogenesis are down-regulated.
- ✓ Decreased mitochondrial function and biogenesis may attributed to the prevalence of Mets in postmenopausal women.
- ✓ Restoration of mitochondrial biogenesis and function may be the therapeutic target of MetS in postmenopausal women.