Clinical trials and Myokines

Hellsten Ylva

Background: Cardiovascular disease is a major cause of death in the western world. Regular physical activity is known to be highly beneficial for improving cardiovascular health status. **Methods**:The current abstract is based on the authors own data and a literature review. The authors own studies have all been accepted by the local ethics committee. In intervention studies the effect of physical training on cardiovascular risk parametres as well as on specific biochemical systems in the cardiovascular system have been studied. Changes in plasma myokine concentrations have been assessed in acute exercise and training interventions in different populations. **Results**: The conducted studies within the cardiovascular area clearly show that regular physical activity is highly beneficial for vascular function and for reducing blood pressure both in aged individuals and in individuals with life style related disease. An ongoing study at The University of Copenhagen conducted in collaboration with Martin Daumer will show to what extent estrogen loss in connection with menopause in women can be replaced by physical activity and thereby retard the progressive risk for cardiovascular disease commonly seen in women after menopause. Many studies have documented that myokines are elevated in response to exercise but more systematic investigations of how specific myokines are altered in response to various types of intensities and duration of exercise and in different subsets of the population is required to more solidly assess their usefulness as markers of physical health status. **Discussion/conclusion**: Based on data from our own studies and studies in the literature, physical activity should be recommended for prevention of cardiovascular disease and should be a primary recommendation in treatment of patients with cardiovascular disease to improve overall cardiovascular health. Use of myokines as markers of health status may be useful but selection of the best markers should await further evidence from systematic studies. <!--[endif]-->

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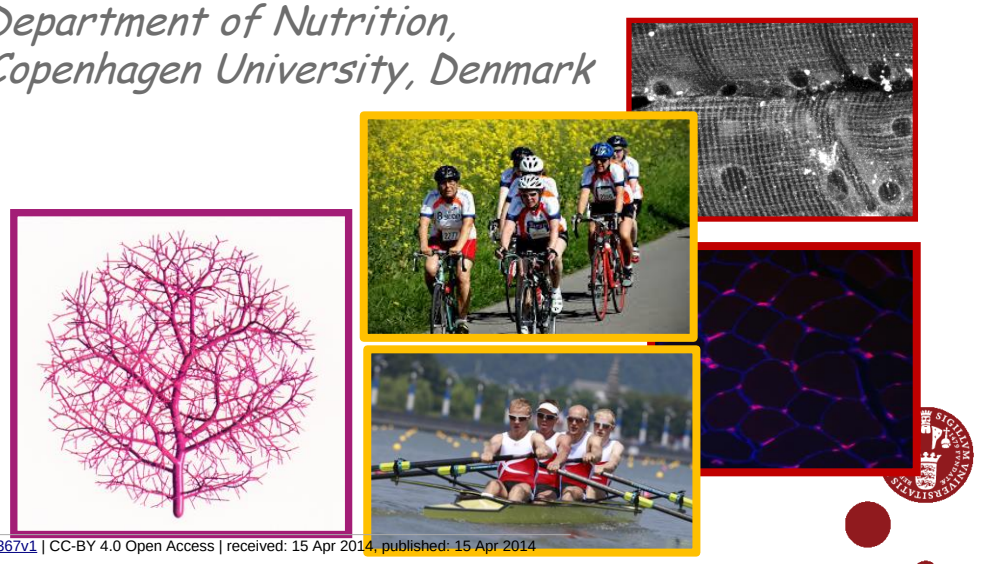
Clinical trials and Myokines

The study of cardiovascular function and health and the impact of physical activity

Can myokines be used as indicators of training/health status?

Ylva Hellsten, Department of Nutrition, Exercise and Sports, Copenhagen University, Denmark



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Cardiovascular function and growth- why are we interested?

Sports performance

- The limits of endurance performance lies in the cardiovascular system

Health-hypertension

- 8 million people die every year in the world on as a consequence of elevated blood pressure

- Approximately 25-40% of the adult Danish population have elevated blood pressure

- Relation to physical activity: For every 2 mm of reduction in blood pressure it is estimated that the risk of death by stroke is reduced by 10 % and the risk of death by ischemic cardiac disease reduced by 7%

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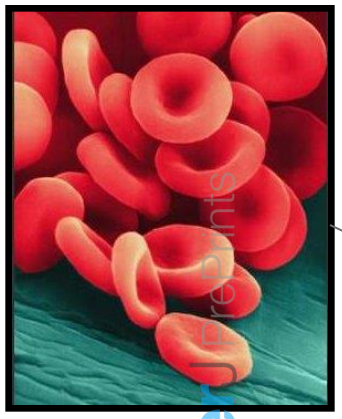
Aspects of the cardiovascular system that we study in man

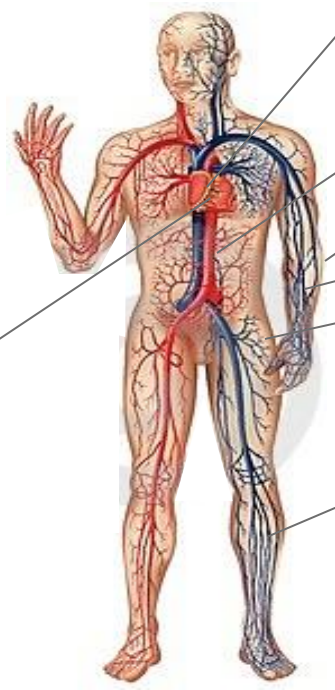
Red blood cells



Oxygen

Platelets

Heart



Arteries

Arterioles

Veins

Venules

Capillaries

A heart pumps out > 200 million liters of blood in a lifetime

Microcirculation

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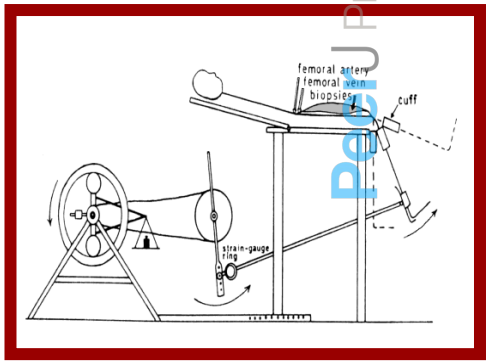
How we study blood flow regulation/vascular function in humans

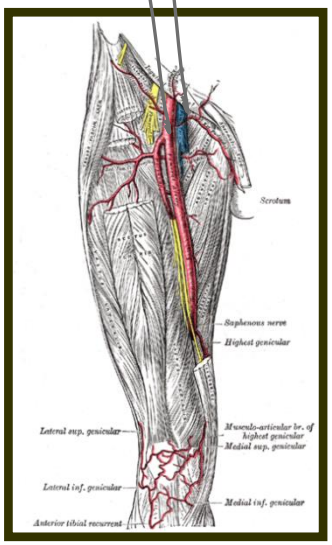
Infusion of compounds

Blood sampling

Knee extensor model



Catheterization



Blood flow measurements

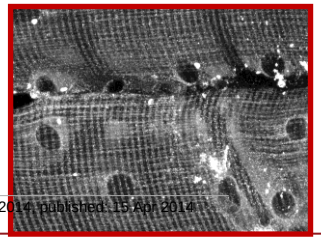
Microdialysis

Pharmacological interventions

Muscle biopsy

Rodents

Microscopy



Cell culture

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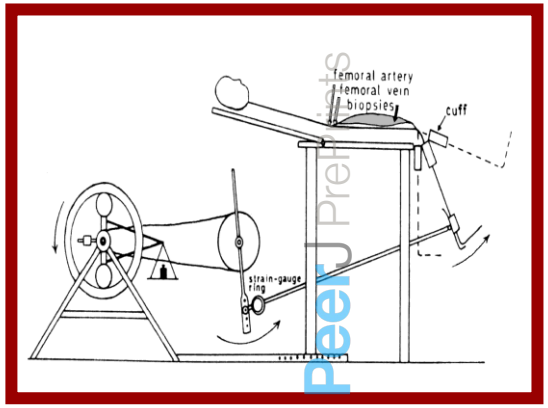
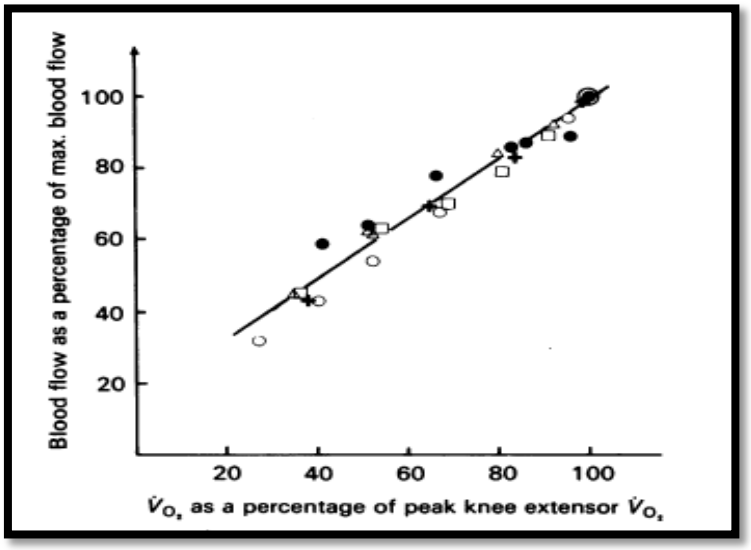
Muscle blood flow in relation to workload: a precise balance between metabolic demand and oxygen delivery



Leg blood flow



Exercise intensity

Saltin et al. 1998

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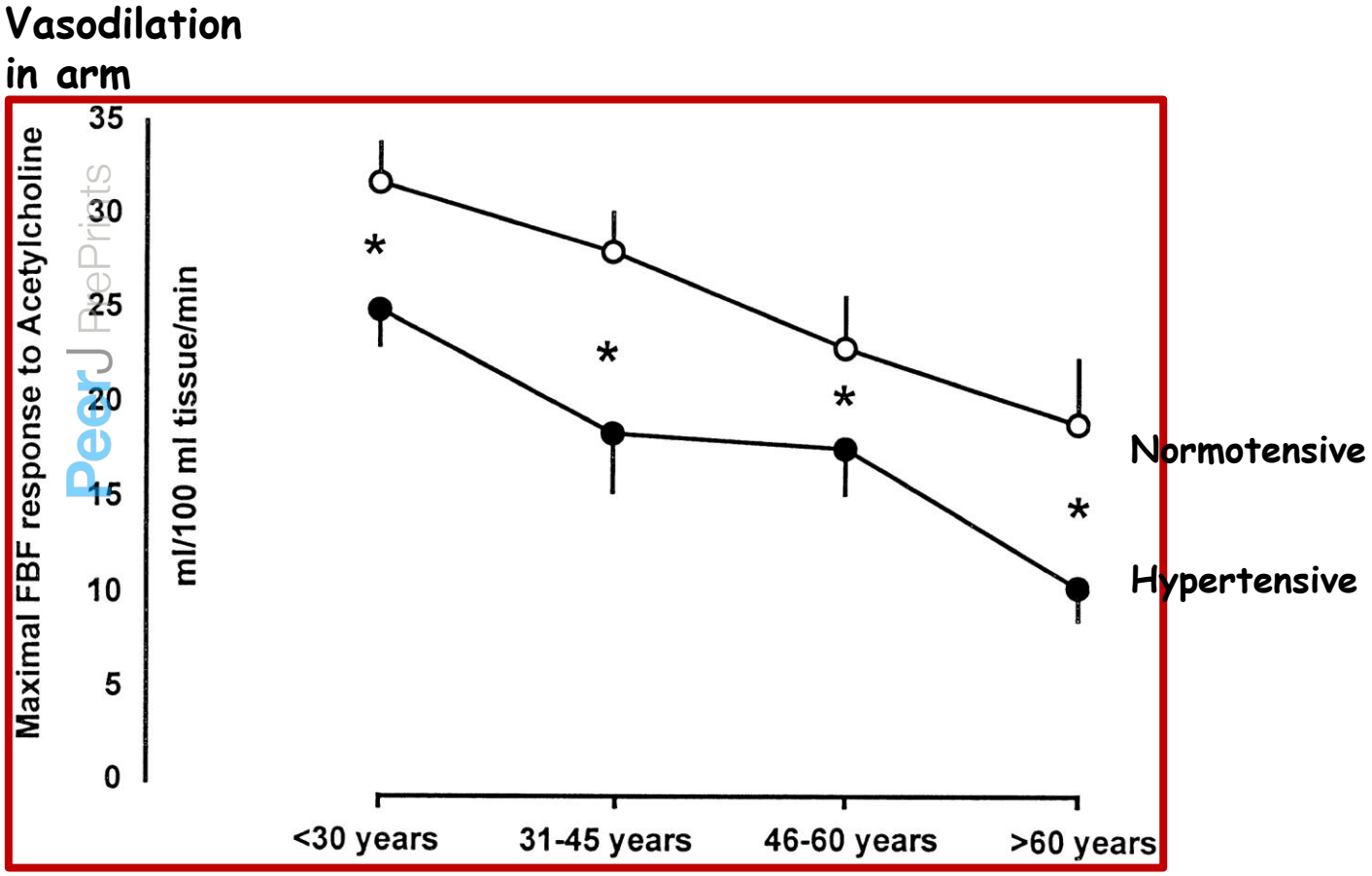
In aging and cardiovascular disease vascular function in the arm is impaired



Taddei, S. et al. Hypertension 1997;29:736-743

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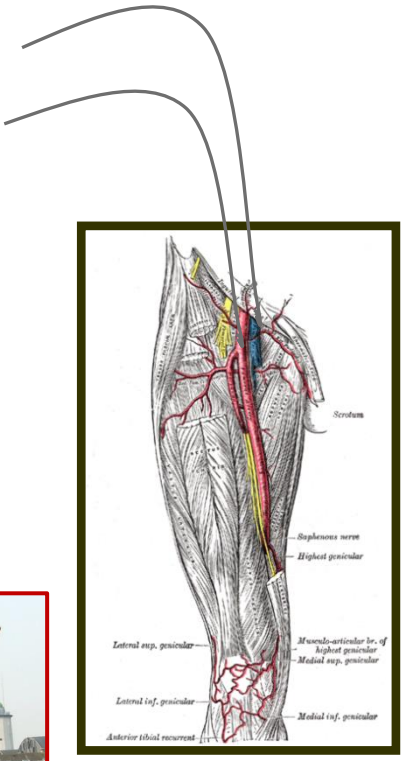
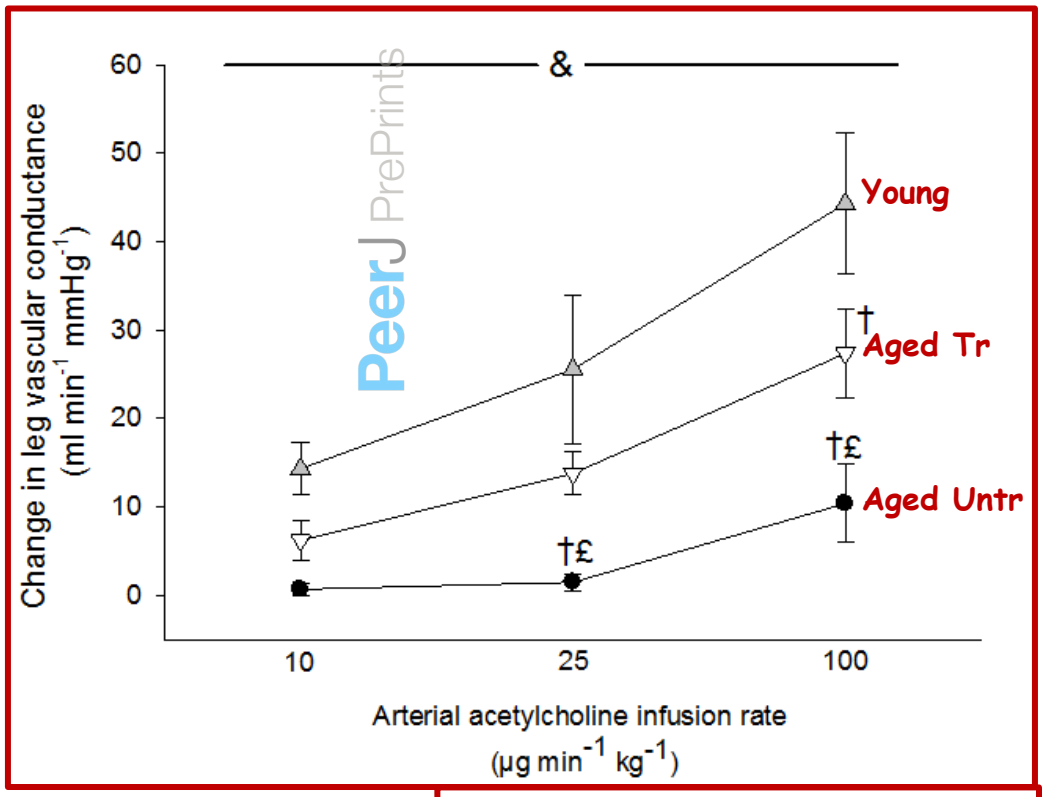
In aging vascular function in the leg is impaired

Infusion of Ach
Blood sampling



Femoral arterial acetylcholine infusion



Nyberg et al. 2012

VO_2 max (ml/min/kg bw)

Young: 45±2
Aged utr: 26 ±1
Aged Tr: 46± 3

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Can you improve cardiovascular health by training in aged individuals- or is it too late?

Training of 27 healthy men 60-65 years of age

Spinning 2 x week + crossfit 1 x week for 8 weeks

Resveratrol supplementation

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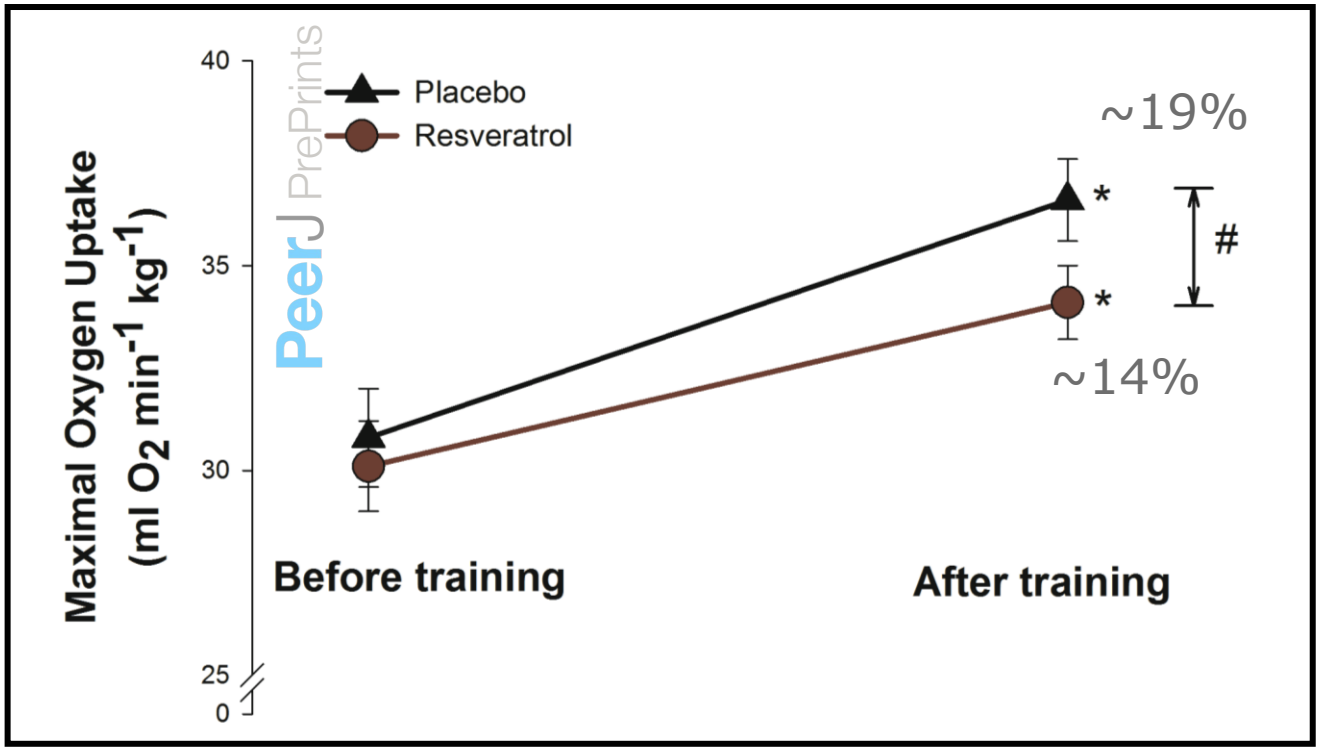
Eight weeks of physical activity increases maximal oxygen uptake in aged sedentary men



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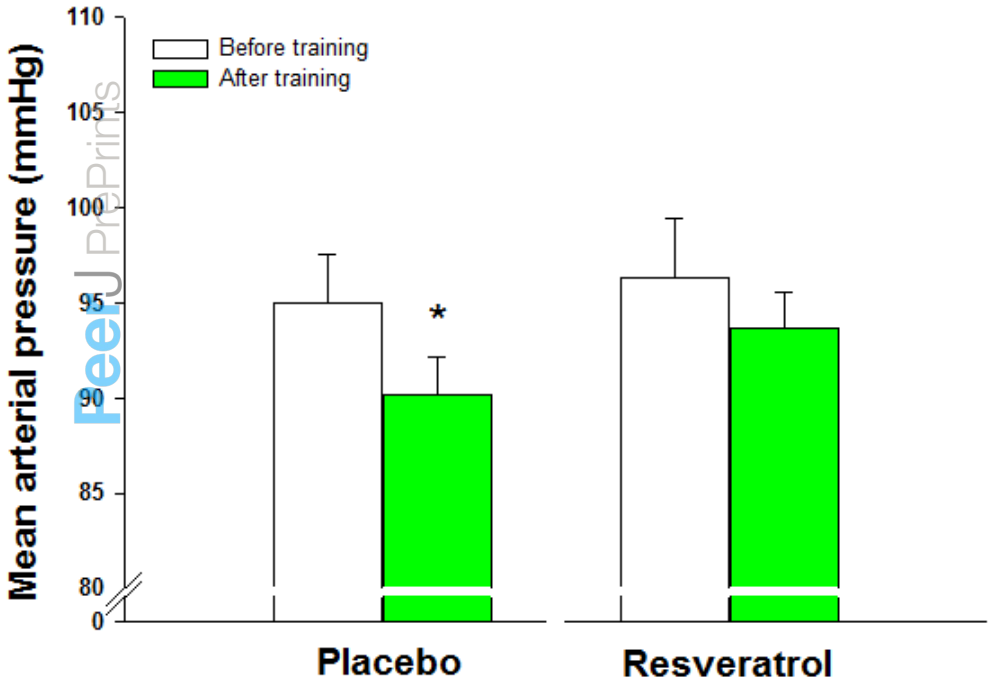
Eight weeks of physical activity lowers mean arterial blood pressure in aged sedentary men



And a number of other parametres related to cardiovascular health were improved by training

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Conclusive remark

Training is highly effective in improving cardiovascular health, including in aging and cardiovascular disease

(but be careful with your supplements)

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Copenhagen Women Study

Women's health during the menopausal transition (45-55 years)

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Background for study

Due to the effects of estrogen, women have a lower risk than men for cardiovascular disease before menopause

After menopause the loss of estrogen

-increases the risk of cardiovascular disease

-increases loss of bone mass

-increases loss of muscle mass

-increases the risk of metabolic disease

Exercise affects similar molecular pathways as estrogen and has marked beneficial effects on health

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Hypotheses of study

Exercise training will limit the adverse effects of estrogen loss on:

-Vascular function and growth

-Cardiac structure and function

-Metabolic status and fat distribution

-Bone density

-Muscle mass

And will improve:

-the level of daily activity

-reduce depression and anxiety

Motivational coaching will have positive effects on adherence to physical activity.

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Collaborative partners outside department:

- Henrik Larsson, Glostrup Hospital, MR scanning
- Charlotte Suetta, Glostrup Hospital, DXA scanning
- Martin Daumer, The Human Motion Institute, Munich, Assessments of daily activities
- Niklas Rye Jørgensen, Glostrup Hospital, bone metabolism,
- Ruth Frikke Schmidt, Rigshospitalet, Genetics
- Lars Bo Nielsen, Rigshospitalet Cardiovascular markers
- Lotte Enevoldsen, Rigshospitalet, Fat and glucose metabolism

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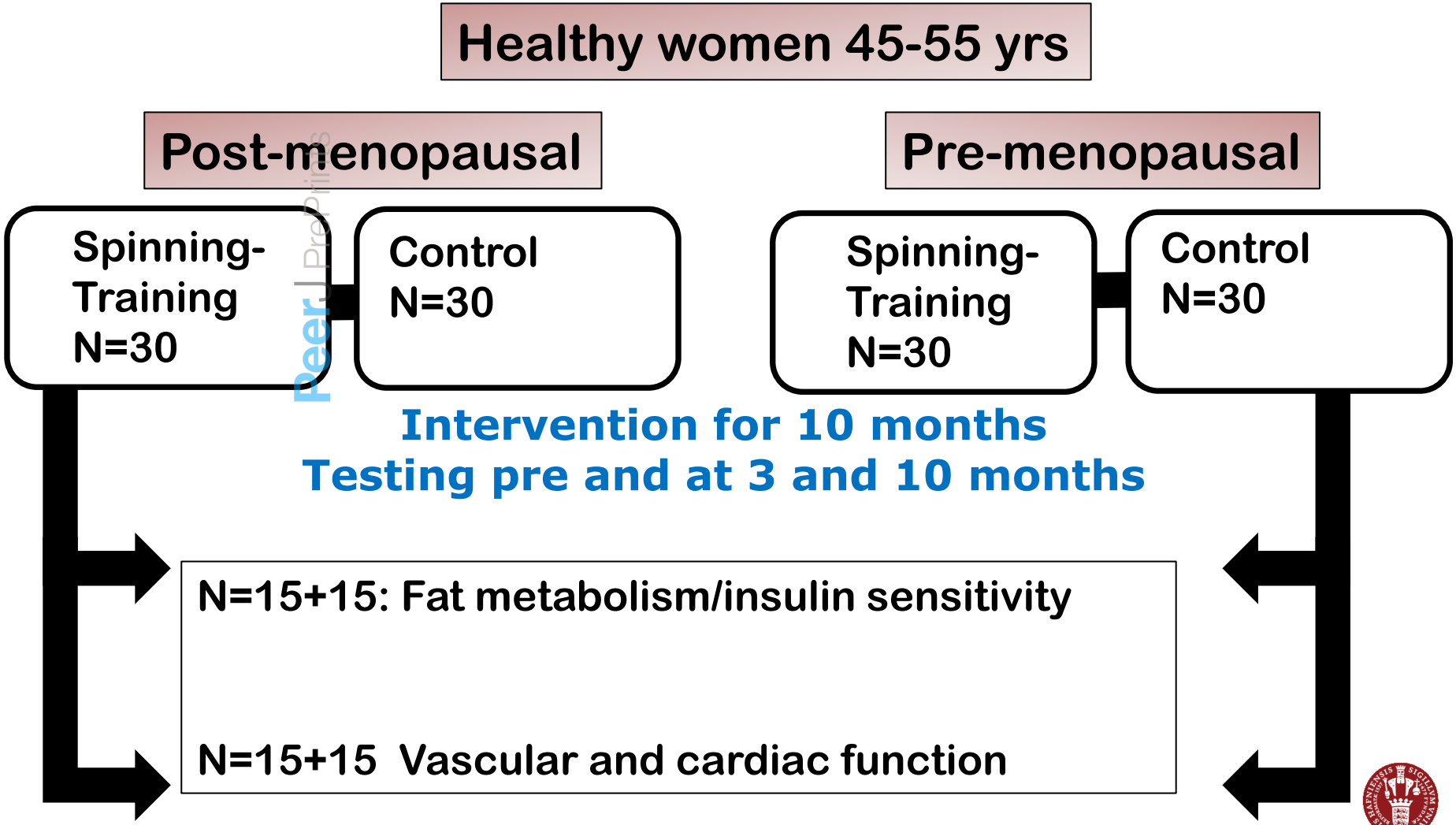
Overall experimental design



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Measured parametres in study





CHARACTERIZATION OF SUBJECTS

- VO_2 max
- Body composition incl bone density
- Plasma lipid status
- Oral glucose tolerance test
- Food registration
- Questionnaires (Social and psychological aspects)
- Muscle and fat biopsies

SPECIFIC ASSESSMENTS

- Assessment of **vascular function** (with focus on prostaglandins)
- Assessment of **cardiac structure and function** (MR and echo doppler)
- Assessment of **angiogenic potential**
- Assessment of **daily activities**
- Assessment of **insulin sensitivity** by euglycemic hyperinsulemic clamp
- Assessment of **fat metabolism**
- Interviews (Sociology)
- Coaching (Psychology)

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Could we use myokines or other compounds for motivational feedback and as markers for training and health status?

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What factors do we associate with health improvements?

- Decreased blood pressure
- Improved vascular function
- Improved cardiac function
- Improved muscle function
- Improved fitness level (maximal oxygen uptake)
- Improved insulin sensitivity
- (Decreased BMI)
- (Increased muscle/fat ratio)

How can we assess these parameters? Or even better, can we find a single representative marker for these parameters?

→ Myokines?

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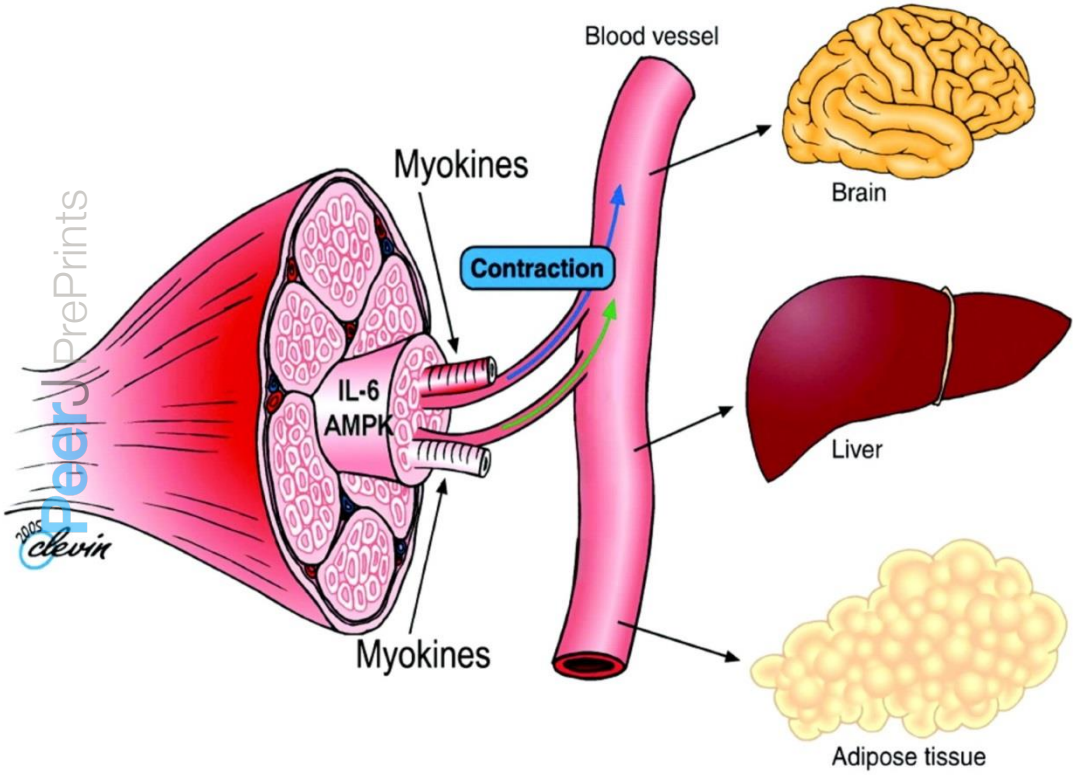
What are myokines?



Pedersen B K J Exp Biol 2011;214:337-346

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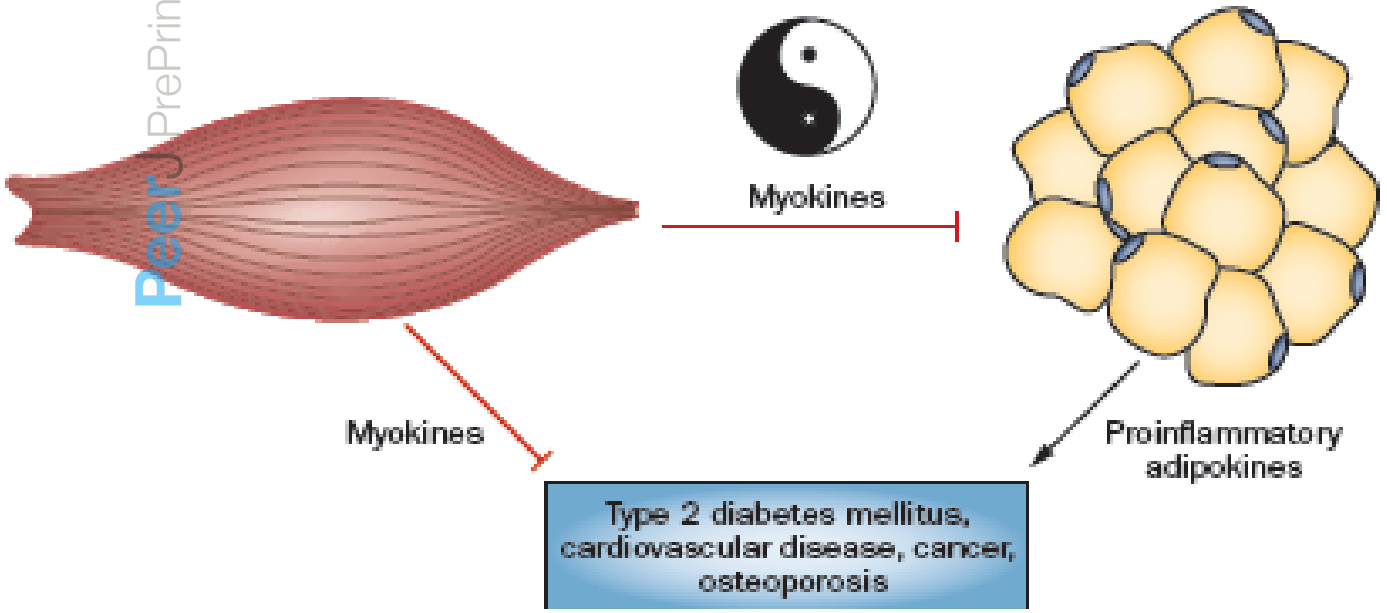
Muscles, exercise and obesity: skeletal muscle as a secretory organ

Bente K. Pedersen and Mark A. Febbraio



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Qualities of a useful exercise/training marker:

- Similar behaviour in different people
- Not too variable by factors other than exercise
- Sufficiently large change in plasma with exercise/training
- Reliable time course
- Easy to conduct reliable measurements
- Should be a motivational marker

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Myokines that increase in plasma after exercise

Myokine	Enhanced serum level after exercise
ANGPTL4	√ [75]
BDNF	√ [63, 64]
FGF21	√ [83]#
FSTL1	√ [112]
IL-6	√ [35]
IL-7	—
IL-8	—
IL-15	√ [49–51] × [52, 165]
Irisin	√ [55, 57] × [56]
LIF	—
MCP-1	√ [32, 69]
Myonectin	√ [86] [88]#
Myostatin	√ [173]#
PAI-1	
PEDF	
VEGF	√ [51]

√: secretion, enhanced regulation of myokine has not been shown. #Myok

Raschke & Eckel, Mediators of Inflammation, 2013

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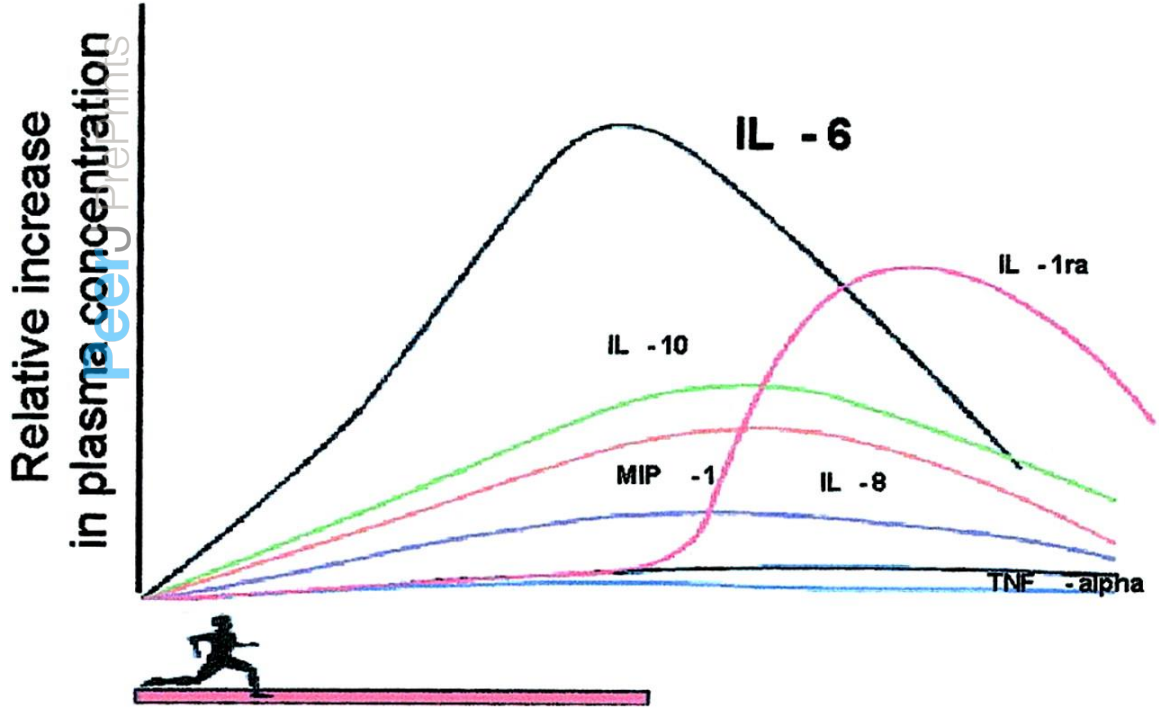
Plasma myokine/cytokine response to strenuous endurance exercise



FEBBRAIO M A, and PEDERSEN B K FASEB J 2002;16:1335-1347

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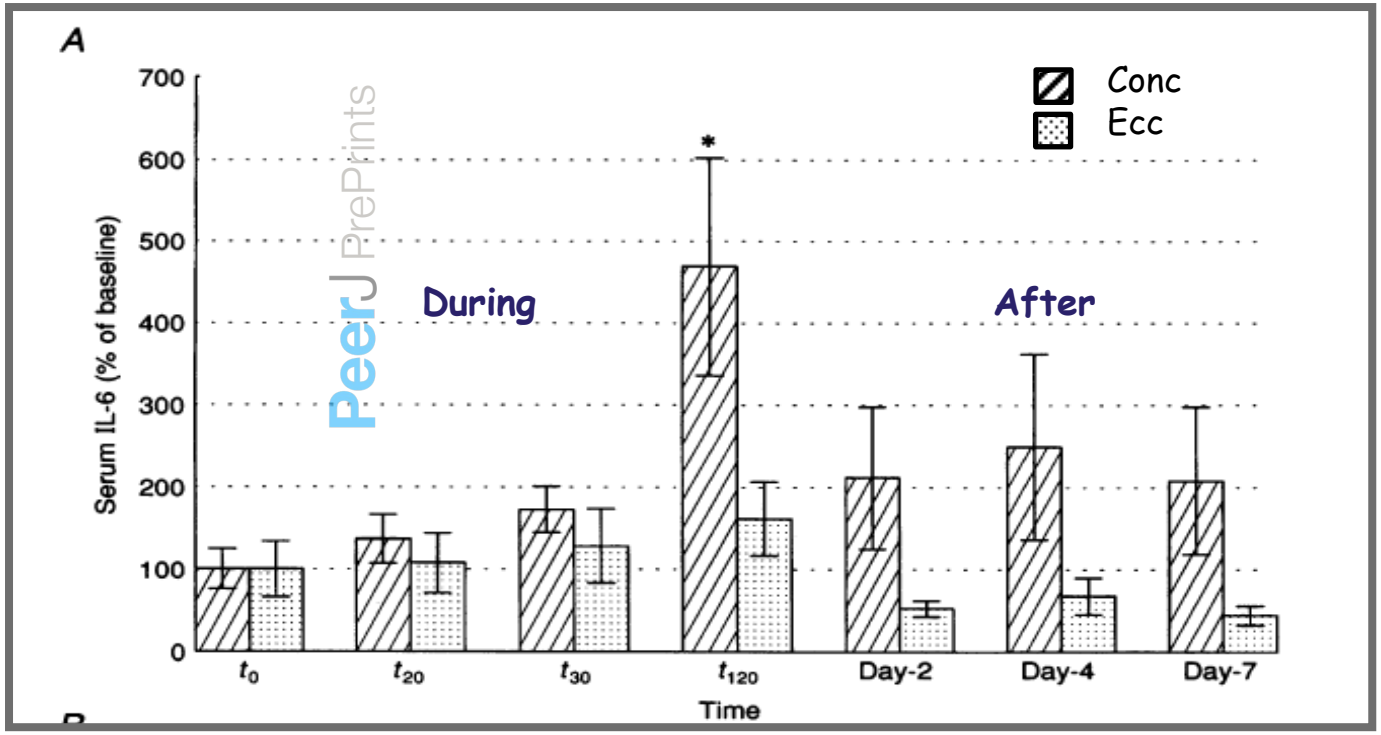
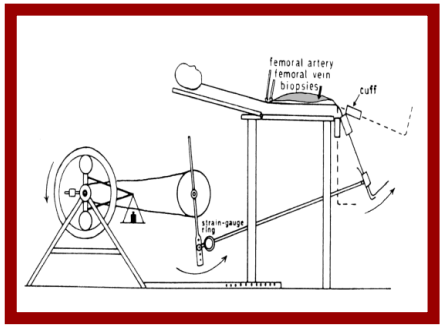
Serum levels of IL-6 after 30 min of concentric or eccentric exercise





Brunsgaard et al. J.Physiol. 1997

Proposed roles of IL-6 in exercise

- Glycogen censor
- Fat oxidation
- Lipolysis
- TNF-α suppressor

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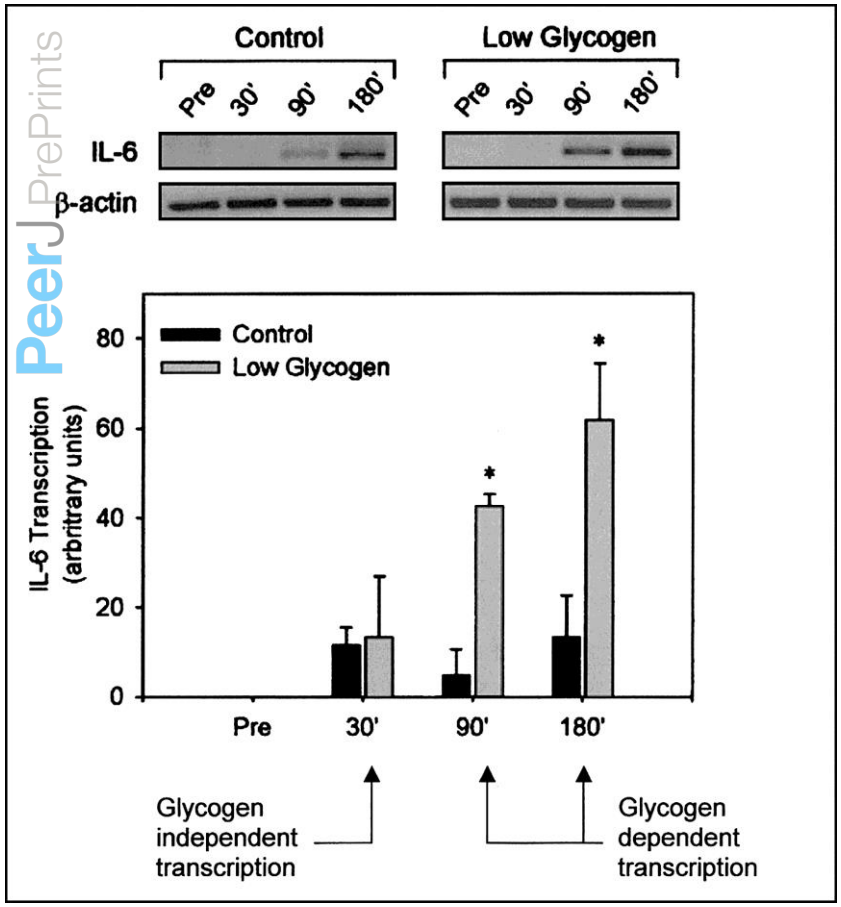
IL-6 transcription in response to exercise-relationship with glycogen levels



FEBBRAIO M A, and PEDERSEN B K FASEB J 2002;16:1335-1347

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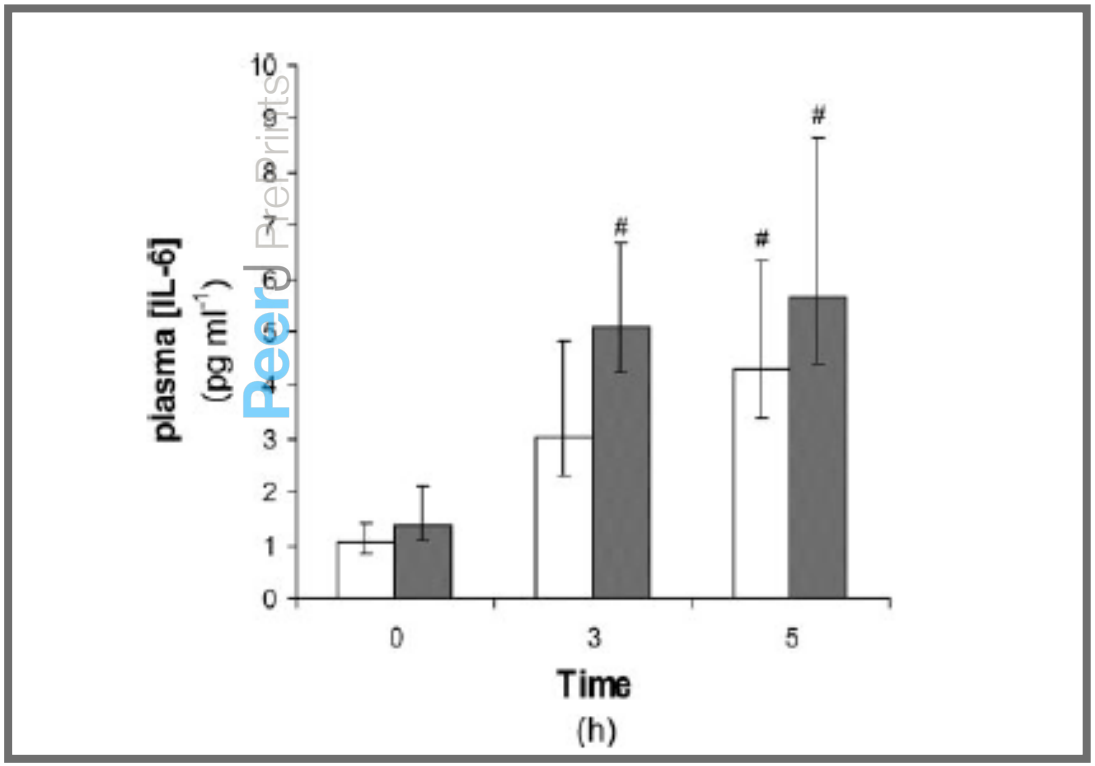
Plasma IL-6 level in response to 3 h of exercise is similar before and after training



Pre training
Post training

Fischer et al. Am J Physiol. 2004

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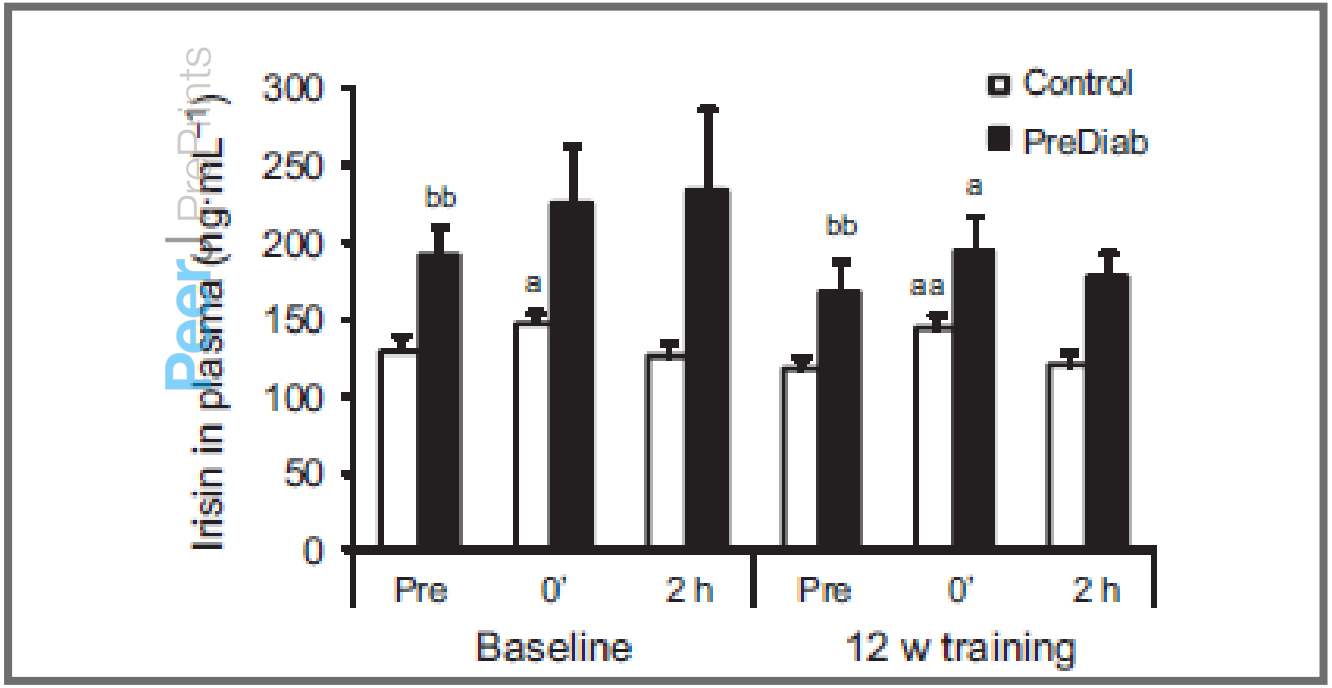
Plasma Irisin in response to 45 min of exercise- effect of training



Proposed role of Irisin

- Browning of fat (leading to increased energy expenditure through dissipation of heat)

Norheim et al. FASEB J, 2014

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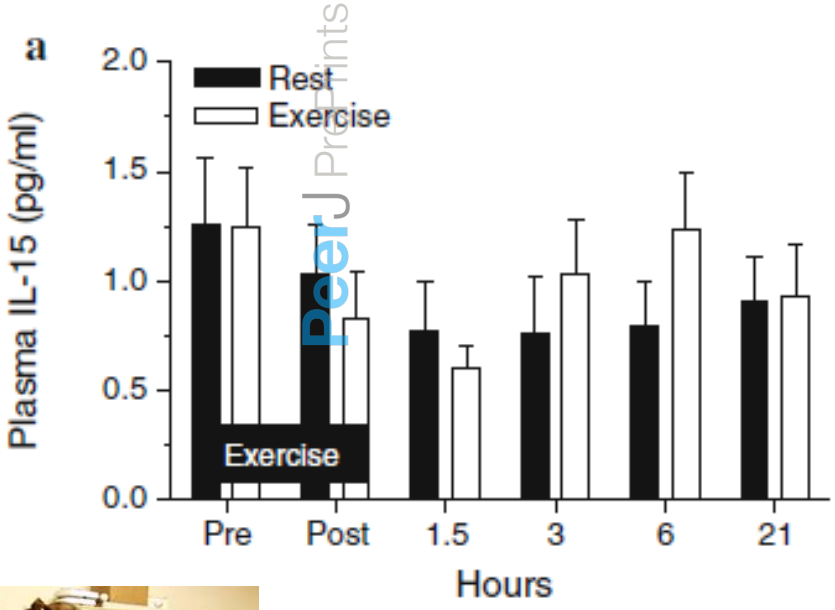
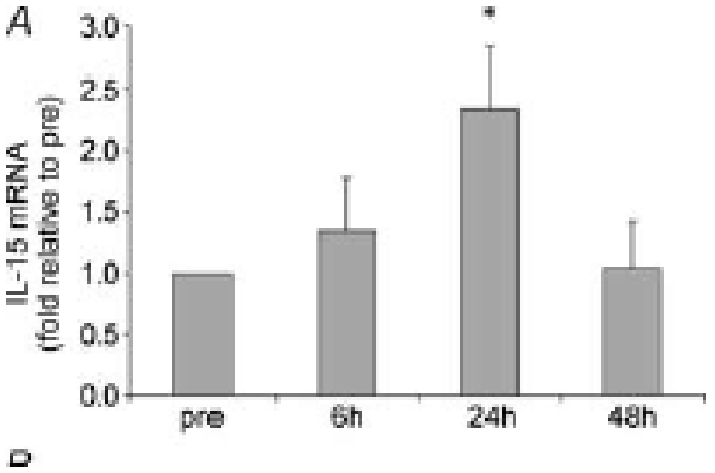
Plasma IL-15 in response to 3 h of cycling exercise



Muscle IL-15 mRNA in response to resistance exercise



Nielsen et al. JPhysiol 2007

<u>Proposed roles of IL-15 in exercise</u>

- Increased hypertrophy of muscle
- Decrease in fat mass

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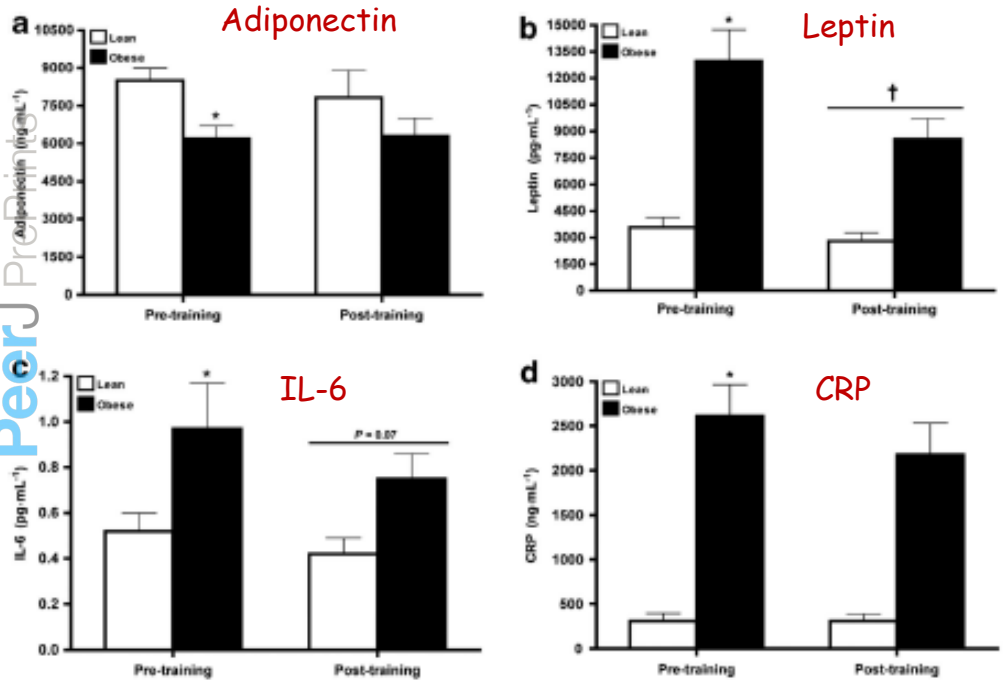
Plasma levels of adiponectin, leptin, IL-6 and CRP before and after training in lean and obese persons

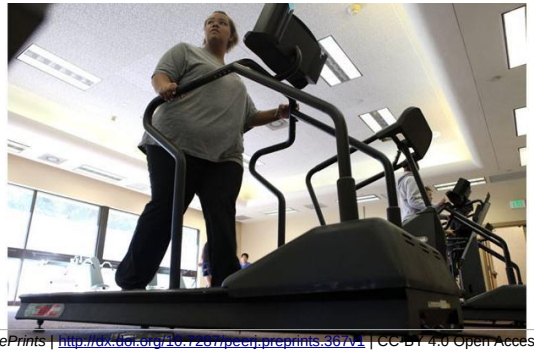
Proposed roles of adiponectin
- Insulin resistance
- Protection of endothelial dysfunction



Proposed roles of Leptin
- Reduces hunger
- Increases energy expenditure

Proposed role of CRP
- Pro-inflammatory

Samjoo et al. 2013



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Parametres associated with health improvements

- Decreased blood pressure
- Improved vascular function
- Improved cardiac function
- Improved muscle function
- Improved fitness level (maximal oxygen uptake)
- (Decreased BMI)
- Improved insulin sensitivity
- (Increased muscle/fat ratio)

Potential indicators

- Fasting blood glucose levels (Glucose)
- Plasma HDL/LDL ratio (HDL/LDL levels)
- Plasma markers of inflammation (Adipokines: leptin, TNFa, PAI-1, Resisitin)
- Plasma markers of atherosclerosis (CRP, VCAM-1, ICAM-1)
- Markers of vascular function (Endothelin-1, follistatin related protein-1)
- Resting heart rate
- Resting blood pressure
- Time trial (walking, running)

Can any **one** of myokines or other markers be used?

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