Can physical exercise and exercise mimetics improve metabolic health in humans?

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The top 10 countries, in numbers of people with diabetes, are:

India
China
USA
Indonesia
Japan
Pakistan
Russia
Brazil
Italy
Bangladesh

Source: Wild et al, 2004
Domino effect:
diabetes increases risk on many complications
Obesity is the major risk factor for type 2 diabetes

> 90% of type 2 diabetes patients is obese!
Ectopic fat accumulation connects obesity with metabolic disorders
Muscle stores lipid droplets
Muscle fat accumulation (IMCL) is negatively associated with insulin sensitivity

Krissak et al., Diabetologia 2002

Sinha et al., Diabetes 2002

Fourouhi et al., Diabetologia 1999

Jacob et al., Diabetes 1999
Lipotoxicity; a delicate balance between oxidation and storage?
Q: Is mitochondrial dysfunction the basis for lipotoxicity?
Knee extension
Against weight

Exercise is performed in MRI scanner during 31P-MRS measurement

Relative PCr content over time (s):
- Rest
- Exercise
- Recovery

Signal intensity (arbitrary units) vs. relative resonance frequency:
- PCr
- Pi
- ATP
Decreased *in vivo* mitochondrial function in T2DM and first-degree relatives

* p<0.05
# p=0.08

Phielix et al., Diabetes 2008
Intrinsic mitochondrial function using high-resolution respirometry

O2 Concentration (A) [pmol/(s*ml)]

State 3

State u

Range [hh:mm:ss]: 00:45:00

vezels mal glut ADP succ FCCP+1+1
intrinsinc mitochondrial function is decreased in T2DM and FDR

No differences in mtDNA copy number

Phielix et al., Diabetes 2008
Conclusion:
Diabetes is associated with lower mitochondrial function in skeletal muscle

Q: does an improved mitochondrial function improve insulin resistance?
12 week endurance and strength training programme

TABLE 1
Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretraining</td>
<td>Posttraining</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.0 ± 0.8</td>
<td>—</td>
</tr>
<tr>
<td>Years since diagnosis</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>94.7 ± 2.7</td>
<td>93.6 ± 2.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>178.5 ± 1.3</td>
<td>—</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.7 ± 0.8</td>
<td>29.4 ± 0.8</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>31.5 ± 1.4</td>
<td>30.6 ± 1.6</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>30.0 ± 1.8</td>
<td>29.2 ± 2.0</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>64.6 ± 2.0</td>
<td>65.4 ± 2.0</td>
</tr>
<tr>
<td>( V_{O2\max} ) (ml · min⁻¹ · kg⁻¹)</td>
<td>28.8 ± 1.0</td>
<td>30.2 ± 1.2*</td>
</tr>
<tr>
<td>Wmax (Watt)</td>
<td>207 ± 10</td>
<td>236 ± 9*</td>
</tr>
<tr>
<td>Average strength (kg)</td>
<td>85.8 ± 3.2</td>
<td>104.0 ± 3.5*</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5.9 ± 0.1</td>
<td>5.5 ± 0.1*</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>5.8 ± 0.1</td>
<td>5.7 ± 0.1*</td>
</tr>
<tr>
<td>Triacylglycerol (mmol/l)</td>
<td>1.52 ± 0.13</td>
<td>1.49 ± 0.15</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE. *Posttraining significantly different from pretraining. †Type 2 diabetes group data significantly different from control group data.
**Study design**

**Screening**

**Baseline measurements**

**Training**

12 weeks

**Post intervention measurements**

**Resistance training:** 1x/week, 8 exercises
1 set, 8 repetitions, 50% of MVC
2 sets, 8 repetitions, 75% of MVC

**Endurance training:** 2x/week.
30 minutes on 55% of max power output

- Progressive training program
- 5 minutes of warming up and cooling down before and after every training session on 45% of max power output on the ergometer
- Supervised training and heart rate monitored
Exercise training improves physical performance

**VO2max/kg body mass**

Data are means ± SE

**Maximal power output**

* Meex et al., Diabetes 2010
Exercise training barely affects body mass or composition

Data are means ± SE
No changes in fat free mass

Meex et al., Diabetes 2010
Exercise training improves metabolic flexibility

Metabolic flexibility ($\Delta$ RER)

$\Delta$ CHO oxidation (g/h)

$\Delta$ Fat oxidation (g/h)

Data are means ± SE

Before training
After training

Meex et al., Diabetes 2010
Exercise training improves mitochondrial function

Mitochondrial function (MRS)

Mitochondrial density

Data are means ± SE

Before training

After training

Meex et al., Diabetes 2010
Exercise training improves insulin sensitivity

Muscle insulin sensitivity

Delta Rd (umol/kg/min)

Before training
After training

Muscle insulin sensitivity

Enogenous glucose production (umol/kg/min)

basal
insulin

Meex et al., Diabetes 2010
Q: What about effects beyond muscle metabolism?
Quantification of cardiac lipid content by $^1$H-MRS

cardiac triggering and breath holds, breathing commands or respiratory gating (resp. sensor or navigator)
Exercise training decreases cardiac lipid content in obese subjects

Schrauwen-hinderling et al., JCEM 2010
Exercise training and metabolic risk

- Not all subjects respond similarly to exercise training
- Subjects with a high baseline ALAT activity (marker of fatty liver) improve more in TG, HDL, VLDL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lower quartile</th>
<th>Upper quartile</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline ALAT (U/L)</td>
<td>24.1±1.3</td>
<td>61.1±2.8</td>
<td>p&lt;0.000</td>
</tr>
<tr>
<td>glucose (mmol/l)</td>
<td>-0.21±0.20</td>
<td>-0.26±0.15</td>
<td>p=0.84</td>
</tr>
<tr>
<td>HBA1c (%)</td>
<td>+0.0±0.09</td>
<td>-0.06±0.07</td>
<td>p=0.62</td>
</tr>
<tr>
<td>FFA (umol/l)</td>
<td>-38±56</td>
<td>-50±40</td>
<td>p=0.86</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>+0.11 ± 0.15</td>
<td>-0.3±0.08</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>total cholesterol (mmol/l)</td>
<td>-0.22±0.13</td>
<td>-0.39±0.24</td>
<td>p=0.53</td>
</tr>
<tr>
<td>LDL (mmol/l)</td>
<td>-0.2±0.09</td>
<td>-0.33±0.21</td>
<td>p=0.57</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td>-0.04±0.03</td>
<td>+0.08±0.04</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>VLDL (mmol/l)</td>
<td>+0.06±0.07</td>
<td>-0.14±0.04</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

*Table 1: changes (before minus after) in cardiovascular risk parameters upon a 12-week training intervention (data are mean±SEM)*

Optimizing the exercise regime for diabetes also needs focus on the liver!
Mitochondrial function

- glucose uptake
- insulin sensitivity
- fatty acid handling
- metabolic flexibility

reduced metabolic risk

Fatty liver

- VLDL-TG output
- FA clearance
- inflammatory lipids
- Glucose output
Conclusion:
Exercise training improves metabolic health

Q: can mitochondrial function be improved without exercise?
Calorie restriction mimetics that target sirtuin 1

• Sirtuin 1 (SIRT1) = NAD\(^+\)-dependent histone deacetylase

• SIRT1 acts as a metabolic sensor, capable of modulating gene expression according to the metabolic state of the cell

• In 2003, Howitz and colleagues performed an \textit{in vitro} screen to identify small molecule activators of SIRT1 and identified \textbf{resveratrol} as the most potent activator (Howitz et al., 2003, Nature)
Resveratrol

- Polyphenolic compound
- Main dietary sources: grapes, wine, peanuts
- Richest source: Japanese knotweed
Can mitochondrial function be improved by functional foods?

Hoeks and Schrauwen, TEM 2012
Resveratrol in rodents

- Prevented weight gain in mice on a high-fat diet
- Improved various biomarkers in the plasma: triglycerides, FFA levels, glucose and insulin values
- Improved insulin sensitivity
- Activated AMPK and SIRT1
- Increased mitochondrial number and decreases acetylation of PGC-1α

→ **Resveratrol shifts the metabolic phenotype of mice on a high-calorie diet towards those on a standard chow diet**

Baur et al., 2006, Nature
Lagouge et al., 2006, Cell
Clinical study design

Timmers et al., Cell Metabolism 2011
### Subjects baseline characteristics (day 0)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Resveratrol</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>52.5 ± 2.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Body weight (kg)</strong></td>
<td>100.1 ± 3.5</td>
<td>99.6 ± 3.7</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>31.59 ± 0.74</td>
<td>31.45 ± 0.82</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Fat (%)</strong></td>
<td>26.44 ± 0.53</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>VO_{2max} (ml.kg^{-1}.min^{-1})</strong></td>
<td>24.96 ± 1.30</td>
<td>24.80 ± 1.00</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mmHg)</strong></td>
<td>131 ± 3.1</td>
<td>132 ± 3.0</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mmHg)</strong></td>
<td>82 ± 2.5</td>
<td>83 ± 2.6</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Glucose (mmol/l)</strong></td>
<td>5.44 ± 0.10</td>
<td>5.44 ± 0.13</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Insulin (mU/l)</strong></td>
<td>16.37 ± 1.76</td>
<td>15.38 ± 2.05</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>TG (mmol/l)</strong></td>
<td>1.86 ± 0.19</td>
<td>1.92 ± 0.21</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>NEFA (µmol/l)</strong></td>
<td>357 ± 69</td>
<td>320 ± 31</td>
<td>0.56</td>
</tr>
</tbody>
</table>
Molecular mechanism of resveratrol

**Figure 2**

**Enrichment plot: REACT_RESPIRATORY ELECTRON TRANSPORT, ATP SYNTHESIS BY CHEMIOSMOTIC COUPLING, AND HEAT PRODUCTION BY UNCOPPLING PROTEINS.**

**Enrichment plot: REACT_CYTOKINE SIGNALING IN IMMUNE SYSTEM.**

**KEGG pathway: oxidative phosphorylation**

Placebo vehicle Mouse RSV

Timmers et al., Cell Metabolism 2011
Molecular mechanism of resveratrol

Timmers et al., Cell Metabolism 2011
Mitochondrial metabolism

state 3, fat oxidation

\[
\text{O}_2 \text{ flux (pmol/mg protein/s) / mtDNA)}
\]

placebo  RSV

state 3, complex I + II

\[
\text{O}_2 \text{ flux (pmol/mg protein/s) / mtDNA)}
\]

<table>
<thead>
<tr>
<th></th>
<th>placebo</th>
<th>resveratrol</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOG</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>MOGS</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>MGS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

state uncoupled

\[
\text{O}_2 \text{ flux (pmol/mg protein/s) / mtDNA)}
\]

placebo  RSV

* Timmers et al., Cell Metabolism 2011
Energy metabolism (day 30)

- SMR (MJ/d)
  - Placebo
  - Resveratrol

- 24h EE (MJ/d)
  - Placebo
  - Resveratrol

- Body weight (kg)
  - Placebo
  - Resveratrol

Timmers et al., Cell Metabolism 2011
Adipose tissue
Ectopic lipid accumulation

![Graph showing relative signal intensity and resonance frequency](image)

![Images of type 1 stain and oil-red-o for placebo and resveratrol](image)

![Bar graphs showing liver fat and muscle fat](image)

Timmers et al., Cell Metabolism 2011
Blood pressure

[Bar graph showing blood pressure levels for systolic, diastolic, and mean arterial pressure under placebo and resveratrol conditions]
### Plasma biochemistry (day 30)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Resveratrol</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/l)</td>
<td>5.28 ± 0.15</td>
<td>5.06 ± 0.13</td>
<td>0.05</td>
</tr>
<tr>
<td>Insulin (mU/l)</td>
<td>11.94 ± 1.11</td>
<td>10.31 ± 1.25</td>
<td>0.04</td>
</tr>
<tr>
<td>HOMA index</td>
<td>2.80 ± 0.20</td>
<td>2.43 ± 0.24</td>
<td>0.03</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>2.29 ± 0.23</td>
<td>2.16 ± 0.21</td>
<td>0.03</td>
</tr>
<tr>
<td>NEFA (μmol/l)</td>
<td>572 ± 77</td>
<td>621 ± 38</td>
<td>0.59</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>14.28 ± 1.98</td>
<td>12.91 ± 1.84</td>
<td>0.04</td>
</tr>
<tr>
<td>Adiponectin (μg/ml)</td>
<td>6.47 ± 0.55</td>
<td>6.45 ± 0.56</td>
<td>0.95</td>
</tr>
<tr>
<td>CRP (ng/ml)</td>
<td>1.52 ± 0.35</td>
<td>1.33 ± 0.31</td>
<td>0.11</td>
</tr>
<tr>
<td>IL-1β (pg/ml)</td>
<td>1.33 ± 0.27</td>
<td>0.94 ± 0.15</td>
<td>0.20</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>3.13 ± 0.67</td>
<td>2.42 ± 0.38</td>
<td>0.09</td>
</tr>
<tr>
<td>IL-8 (pg/ml)</td>
<td>4.94 ± 0.59</td>
<td>4.28 ± 0.25</td>
<td>0.19</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>16.15 ± 2.27</td>
<td>15.14 ± 2.03</td>
<td>0.04</td>
</tr>
<tr>
<td>Leukocytes (10⁹/l)</td>
<td>7.03 ± 0.44</td>
<td>6.48 ± 0.39</td>
<td>0.03</td>
</tr>
<tr>
<td>ALAT (U/l)</td>
<td>31.91 ± 2.21</td>
<td>28.09 ± 1.54</td>
<td>0.02</td>
</tr>
</tbody>
</table>
There is more than resveratrol: central role for nutritional sensors in regulating mitochondrial function
Acipimox – a lipolysis inhibitor - increased rather than decreased FFA: rebound effect

Type 2 diabetic patients treated with acipimox or placebo for 2 weeks

Example of ORO staining in 1 patient
Acipimox – a NAD+ analogue – increases muscle mitochondrial function in humans

C2C12

Van de Weijer et al., Diabetes 2014
Conclusion:

Mitochondrial function can be improved by NAD+ boosters, also in humans

Clinical intervention studies are needed to test if NAD+ is a target to prevent/treat type 2 diabetes
Stimulating energy turnover as a target to improve metabolic health

Dietary fat

Storage

Fat

Oxidation