Optimizing the Exercise Drug to Oppose Glucose Intolerance/T2D

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Lab mission: Metabolic rehabilitation

Understand how physical activity, diet and pharmacology can be optimally integrated to reverse insulin resistance and prevent T2D
79 million with prediabetes = everyone in U.S. that is left-handed (30) + everyone who is Jewish (6) + all households in U.S. that own dogs (43).

Insulin resistance is an underlying theme for Type-2 diabetes (as well as CVD)
Insulin Resistance

LIVER

islet cells

MUSCLE

FAT

CNS
Diabetes Prevention Program, NEJM, 2001

>150’ exercise/wk. goal to lose 7% BW.
Lifestyle change

Weight loss

beneficial impact on metabolic health

Metformin
Mean weight loss: 3.3 kg

Activity maintained at about 150’/wk
Lifestyle change

Weight loss

habitual activity

beneficial impact on metabolic health

Metformin
Single dose

King et al., JAP, 1995
Lifestyle change

Weight loss

exercise training

beneficial impact on metabolic health

acute exercise

Metformin
Exercise as drug

At sufficient dose, exercise improves metabolic function for a period of time but the effect wanes, requiring subsequent doses.

Tailoring dose to achieve maximal effect is likely to result in biggest long-term reward.
What do we need to know?

Dose:
- Threshold ($\approx 150$ min/week)
- Frequency (3+ d/wk)
- Intensity/Duration (HIIT, sedentary time?)

Interactions with diet

Interactions with other medications
No-Exercise

LO = 3 bouts at 50% VO$_2$max, = 750 kcal
HI = 3 bouts at 75% VO$_2$max, = 750 kcal

Braun et al. J Appl. Physiol. 1995
Interactions with diet: Energy balance?

16 men and women

Energy Deficit “DEF”

Energy Balance “BAL”

Weight Maintenance Period

Pre-Training Insulin Action

6 DAYS OF

EXERCISE

Post-Training Insulin Action
<table>
<thead>
<tr>
<th></th>
<th>DEF</th>
<th>BAL</th>
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</thead>
<tbody>
<tr>
<td>Energy Ingested (kcal)</td>
<td>2246 ± 97</td>
<td>2925 ± 159</td>
</tr>
<tr>
<td>Estimated Energy Expenditure (kcal)</td>
<td>2727 ± 182</td>
<td>2917 ± 169</td>
</tr>
<tr>
<td>Energy Balance (kcal)</td>
<td>-481 ± 24</td>
<td>+8 ± 20</td>
</tr>
<tr>
<td>Weight Change (kg)</td>
<td>-0.62 ± 0.2</td>
<td>+0.03 ± 0.2</td>
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All food provided, EE derived from RMR, accelerometers, food, activity records
Whole-body and hepatic insulin action (CIG-SIT)

90 min [6,6 \( ^2 \)H] glucose

| Change infusate | 60 min (20% glucose + 2% [6,6 \( ^2 \)H] glucose) |

Fasted state

Steady-state

Outcomes: whole-body glucose uptake and suppression of liver glucose output
Black et al. J Appl Physiol, 2005

Glucose

Muscle

Rd (μM/kg FFM/min)/SS Ins

Pre

Post

DEF

BAL

*
Energy balance the only difference?

CHO content of diets in 2 groups different.

DEF = 330 g CHO/day; BAL = 410 g/day.

Meal (60% CHO) immediately post-exercise
Weight loss

Lifestyle change

Pharmacology

exercise training

acute exercise

energy balance

meal CHO

timing

beneficial impact on metabolic health
Diabetes Prevention Program, NEJM, 2001

Lifestyle + metformin = even better?
Exercise and metformin

**Purpose:** Combined effect of metformin and acute exercise on insulin sensitivity and AMPK α2

**Hypothesis:** $1 + 1 = 2$
Metformin group: pre-Met, Met + rest, post Met + Ex
Placebo group: rest, exercise

| Overnight Fast | 40 min rest or exercise | BIOPSY | 90 min. stable isotope [6,6-2H] glucose infusion | Euglycemic hyperinsulinemic clamp |

Percutaneous biopsy of vastus lateralis

Blood sampling

Goodyear lab for analyses of AMPK activity, glycogen, and western blots.
Sharoff et al., Am J Phys, 2010
Sharoff et al., Am J Phys, 2010

The diagram illustrates the AMPK alpha 2 activity (pmol/mg/min) for placebo and metformin treatments. The bars show a comparison between the two conditions, with metformin generally leading to a higher AMPK alpha 2 activity than placebo.
Does metformin blunt beneficial effects of training?

32 men and women with prediabetes

12 wks training with or w/o metformin, metformin only and control

Insulin sensitivity using clamp and tracers
Insulin sensitivity enhanced more with exercise alone than when combined with metformin

Malin et al. Diabetes Care, 2011
Non glycemic outcomes

SBP:
C = +6.5%, M = -7.3%, EP = -6.3%, EM = 0.0%

hs-CRP:
C = +6.4%, M = -20.1%, EP = -27.4%, EM = -8.4%

TAG:
C = +3.1% M = -13.8%, EP = -13.5%, EM = -12.0%

Malin et al. Obesity, 2012
Why?

Wt? Only M and E+M lost weight
Fat? M = nc, E+M and E+P = -2%
Central fat? M = nc, E+M and E+P = -1.5%

CRF? M = nc, E+M ≈ +10%, E+P ≈ +20%

ΔVO2peak and Δinsulin sensitivity: r = .70
Weight loss

Lifestyle change

exercise training

acute exercise

metformin

energy balance

meal CHO

timing

beneficial impact on metabolic health
Role of “sedentary behavior” in mediating efficacy of the exercise drug??
14 normally active men and women
3 conditions, balanced order

Active, energy bal (no sit 15 hr.)

Inactive (sit 15 hr, no diet change)

Inactive, (sit 15 hr, cut kcals)
Sedentary subjects
Control, 12 wks training (EX), reduced sedentary time (rST) OR both (EX+rST).

EX+rST accentuated impact of EX alone
C-ISI up by 24% vs. 17.5% (but TG same)

Little impact of rST alone
Weight loss

Lifestyle change

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metformin

Weight loss

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beneficial impact on metabolic health
Conclusions

At sufficient dose, exercise/physical activity potent countermeasure

Less sedentary behavior useful but not sufficient

Interxns between exercise and nutritional context

Interactions with other meds NOT predictable
beneficial impact on metabolic health