May 20th, 2:30 PM

Optimizing the Exercise Drug to Oppose Glucose Intolerance/T2D

Barry Braun
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Optimizing the Exercise Drug to Oppose Glucose Intolerance/T2D

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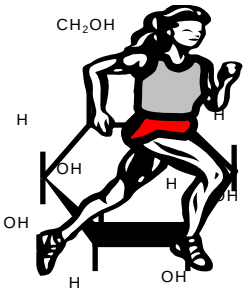
Lab mission:
Metabolic rehabilitation

Understand how physical activity, diet and pharmacology can be optimally integrated to reverse insulin resistance and prevent T2D

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New Mexico
North Dakota
South Dakota
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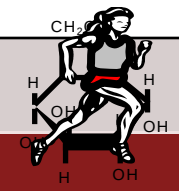
Oklahoma
Texas
Minnesota
Iowa
Missouri
Arkansas
Louisiana
Wisconsin
Illinois
Michigan
Indiana
Ohio
Kentucky
Tennessee
Mississippi
Alabama
Georgia
Florida
South Carolina
North Carolina
Virginia
West Virginia
Pennsylvania
New York
Maryland
Delaware
New Jersey
Connecticut
Rhode Island
Massachusetts
Vermont
New Hampshire
Maine
Washington, D.C.
Alaska
Hawaii

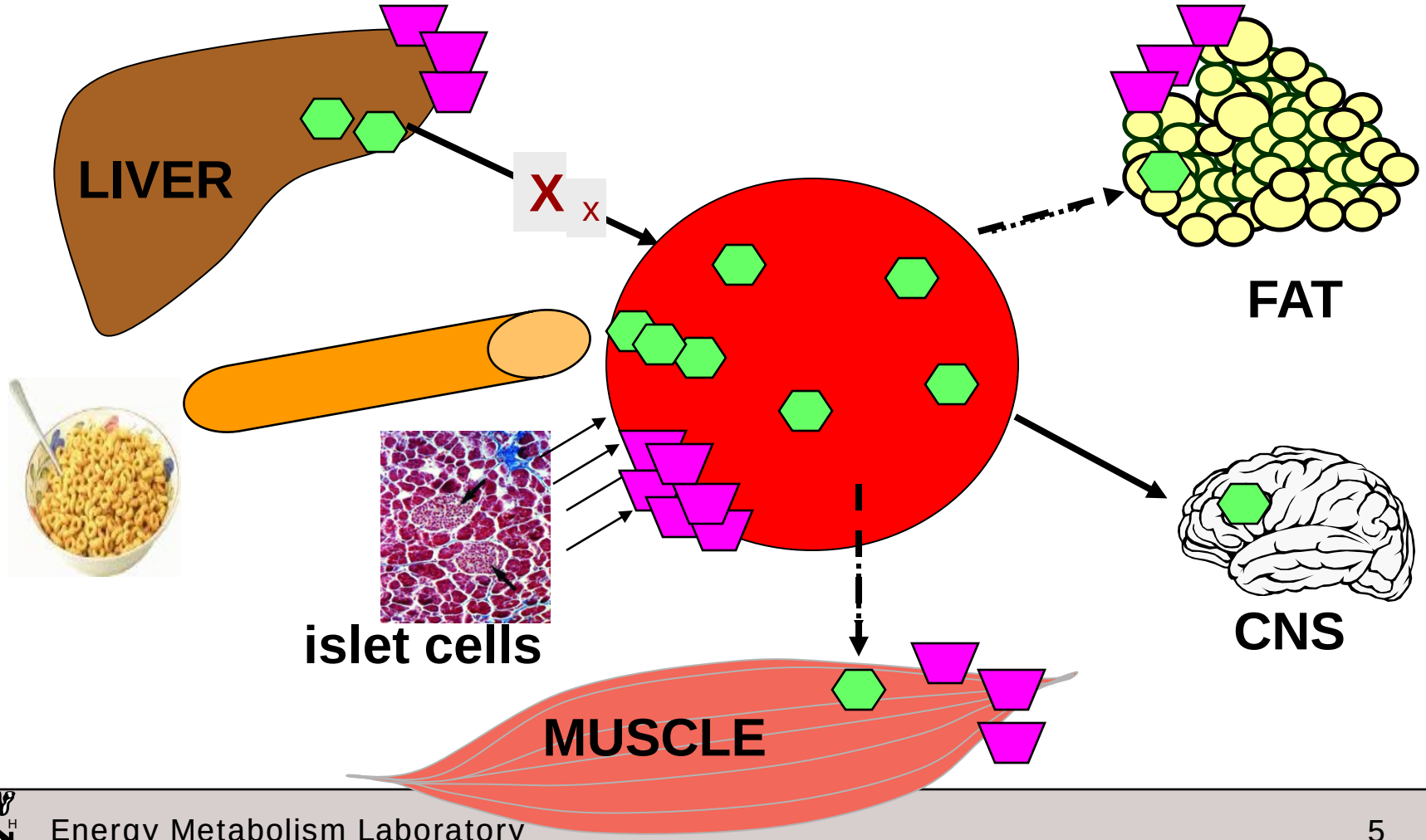
79 million with prediabetes=

everyone in U.S. that is left-handed (30) +
everyone who is Jewish (6) +
all households in U.S. that own dogs (43).

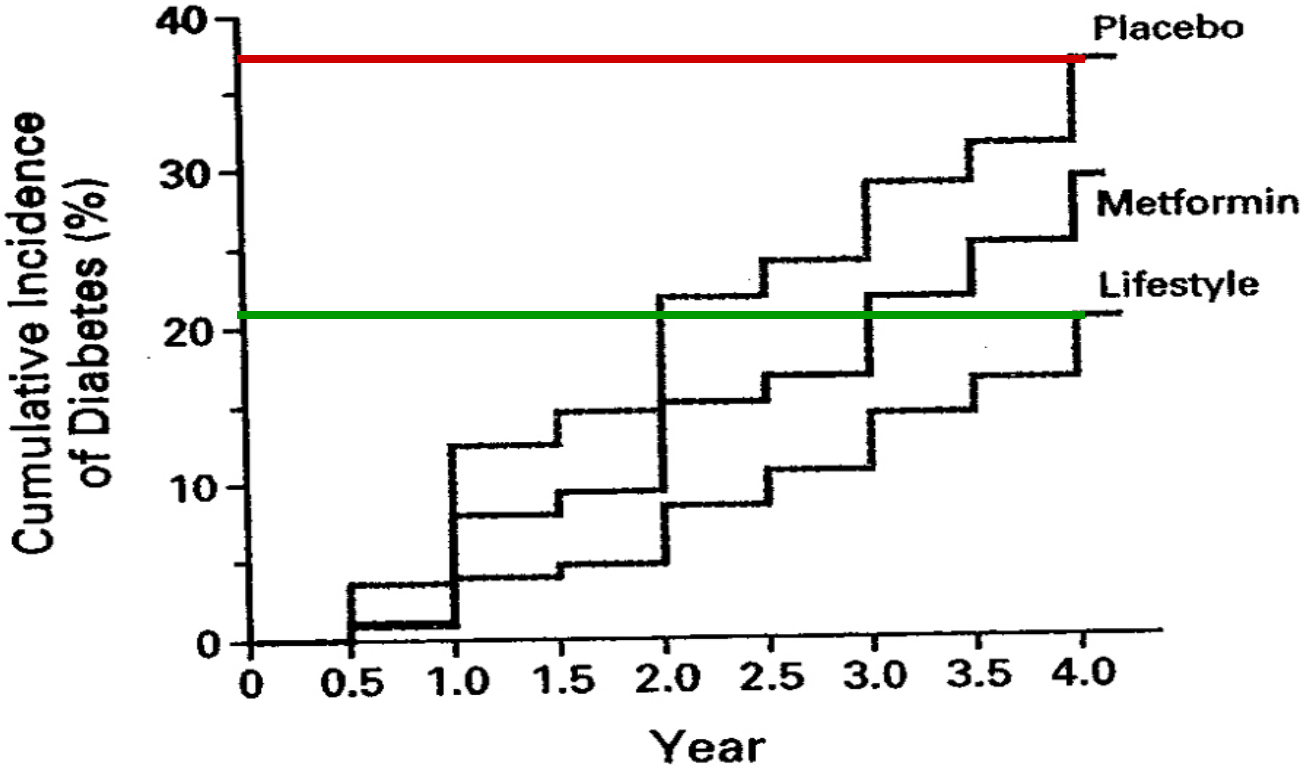
Insulin resistance is an underlying theme for Type-2 diabetes (as well as CVD)



Insulin Resistance



Diabetes Prevention Program, NEJM, 2001



>150' exercise/wk. goal to lose 7% BW.

Lifestyle change

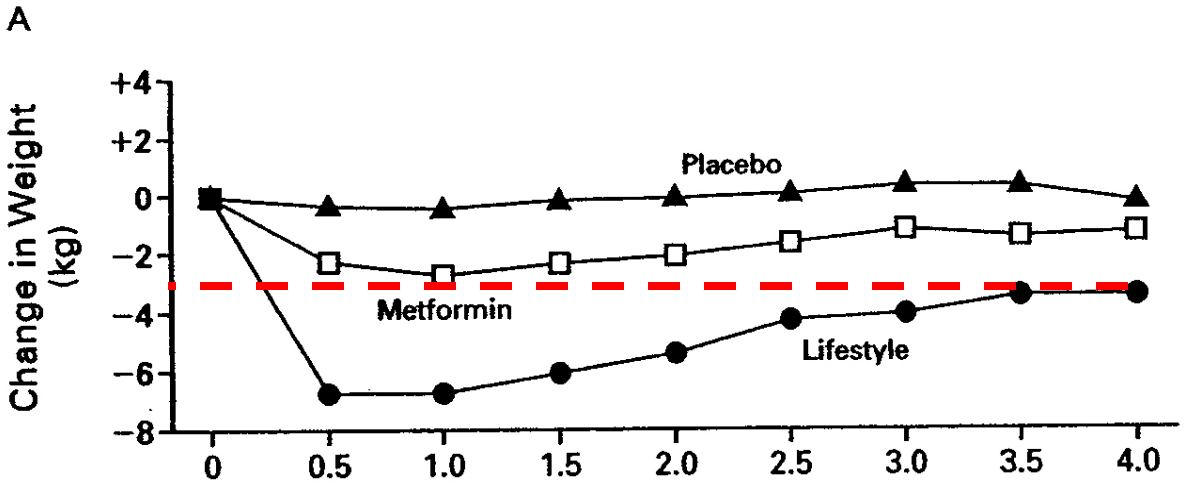
Metformin

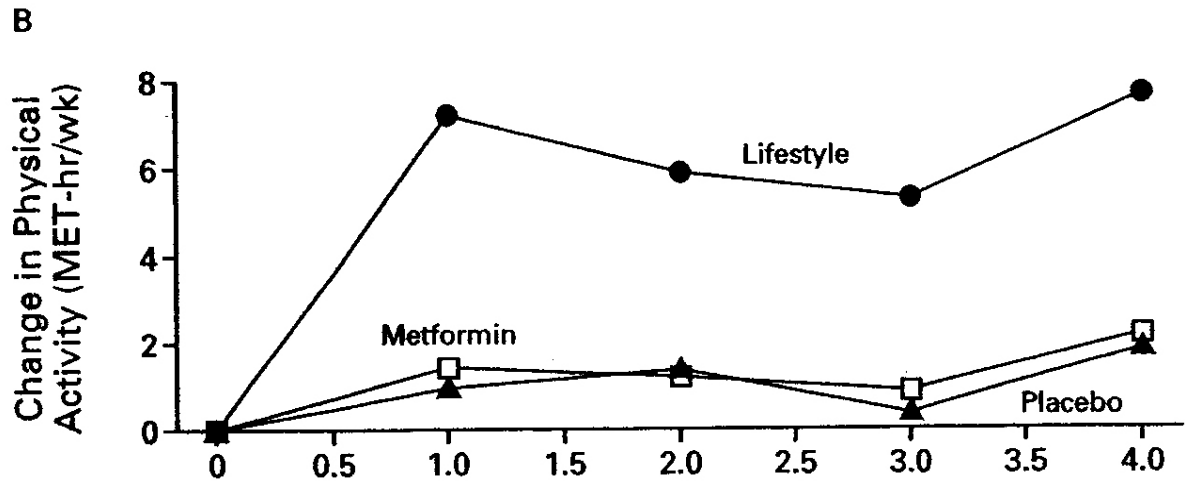
Weight loss

beneficial impact on metabolic health

Mean weight loss: 3.3 kg

Activity maintained at about 150’/wk





C

Lifestyle change

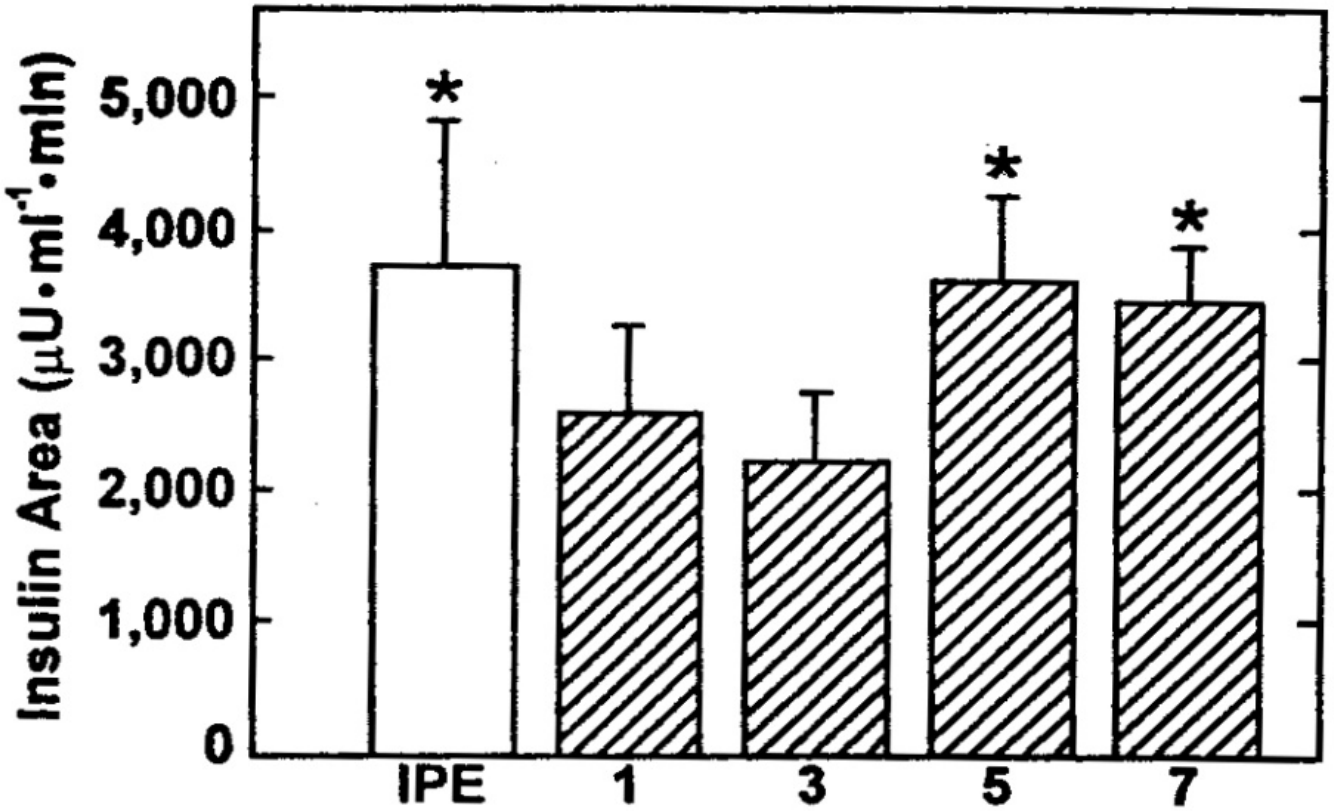
habitual activity

Metformin

Weight loss

beneficial impact on metabolic health

Single dose



King et al., JAP, 1995

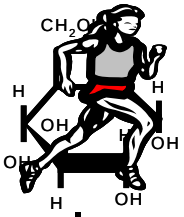
Lifestyle change

Metformin

exercise training

acute exercise

Weight loss

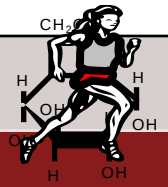


beneficial impact on metabolic health

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



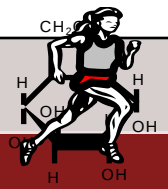
What do we need to know?

Dose:

- Threshold (≈ 150 min/week)
- Frequency (3+ d/wk)
- Intensity/Duration (HIIT, sedentary time?)

Interactions with diet

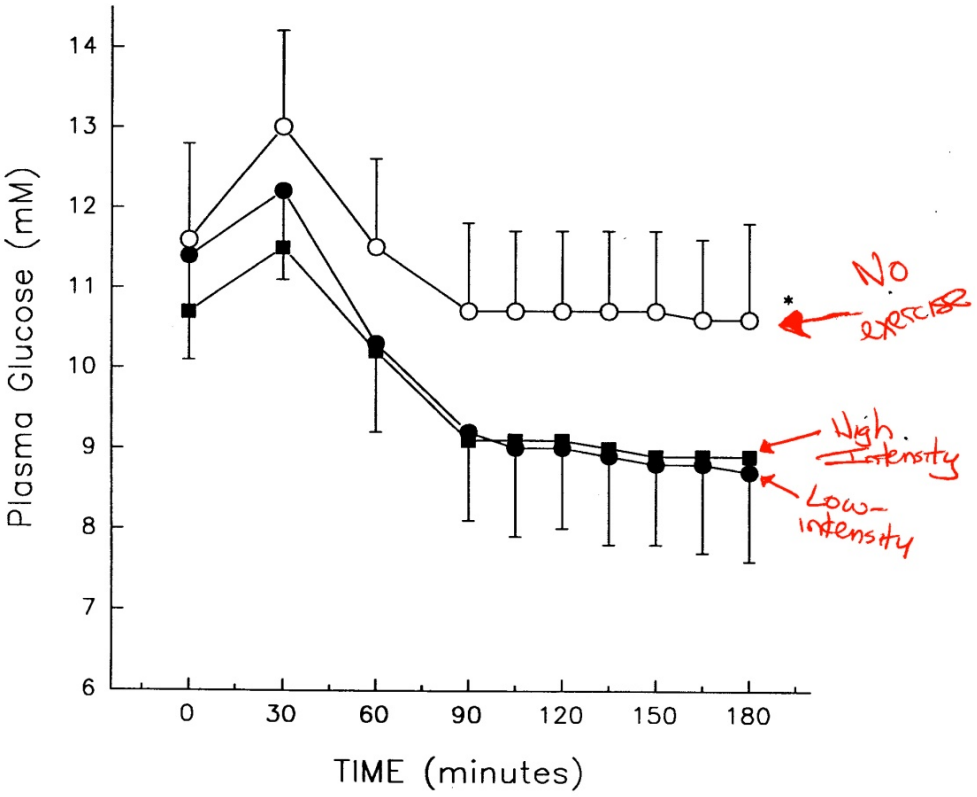
Interactions with other medications



No-Exercise

LO = 3 bouts at 50% VO_2max,= 750 kcal

HI = 3 bouts at 75% VO_2max,= 750 kcal



Braun et al. J Appl. Physiol. 1995

Interactions with diet: Energy balance?

16 men and women

→ **Energy Deficit "DEF"**

→ **Energy Balance "BAL"**

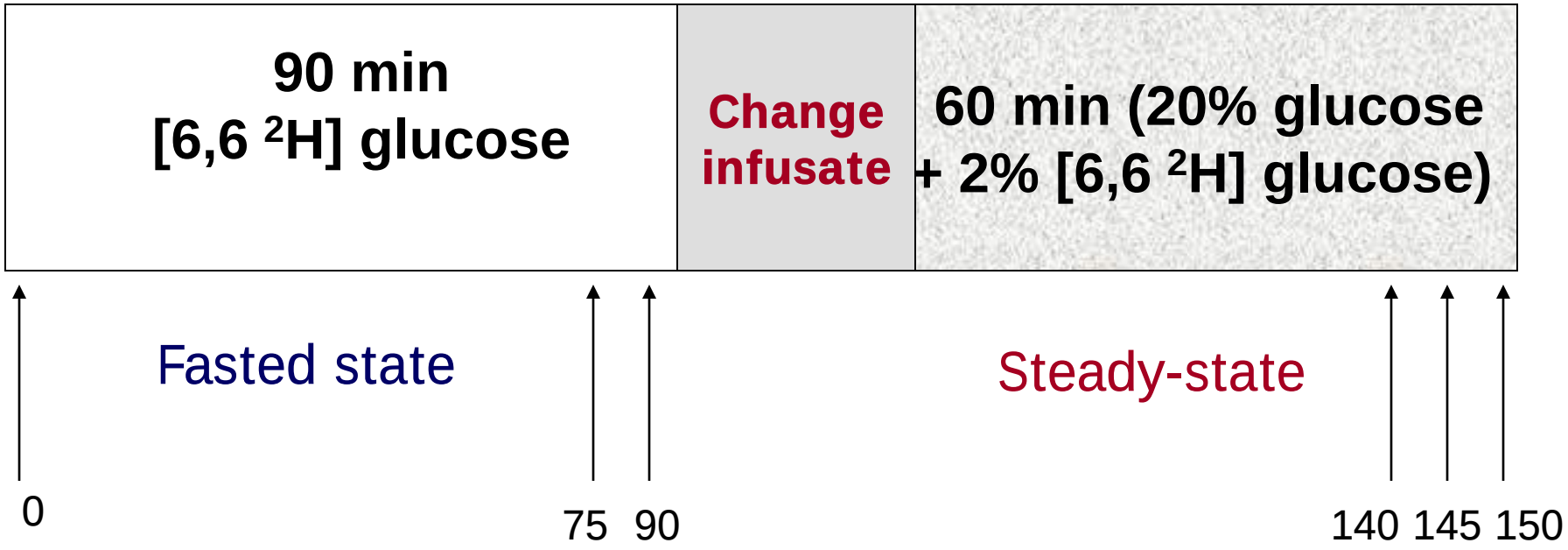
Weight Maintenance Period

Pre-Training Insulin Action → **6 DAYS OF EXERCISE** → **Post-Training Insulin Action**

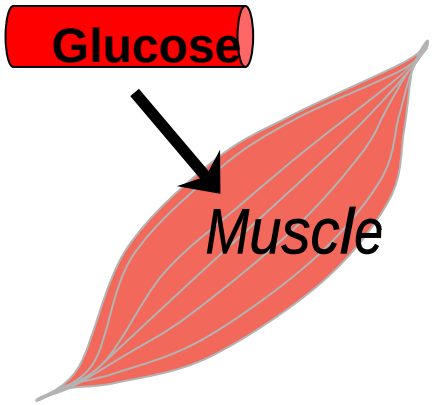
	DEF	BAL
Energy Ingested (kcals)	**2246 ± 97**	**2925 ± 159**
Estimated Energy Expenditure (kcal)	**2727 ± 182**	**2917 ± 169**
Energy Balance (kcal)	**-481 ± 24**	**+8 ± 20**
Weight Change (kg)	**-0.62 ± 0.2**	**+0.03 ± 0.2**

All food provided, EE derived from RMR, accelerometers, food, activity records

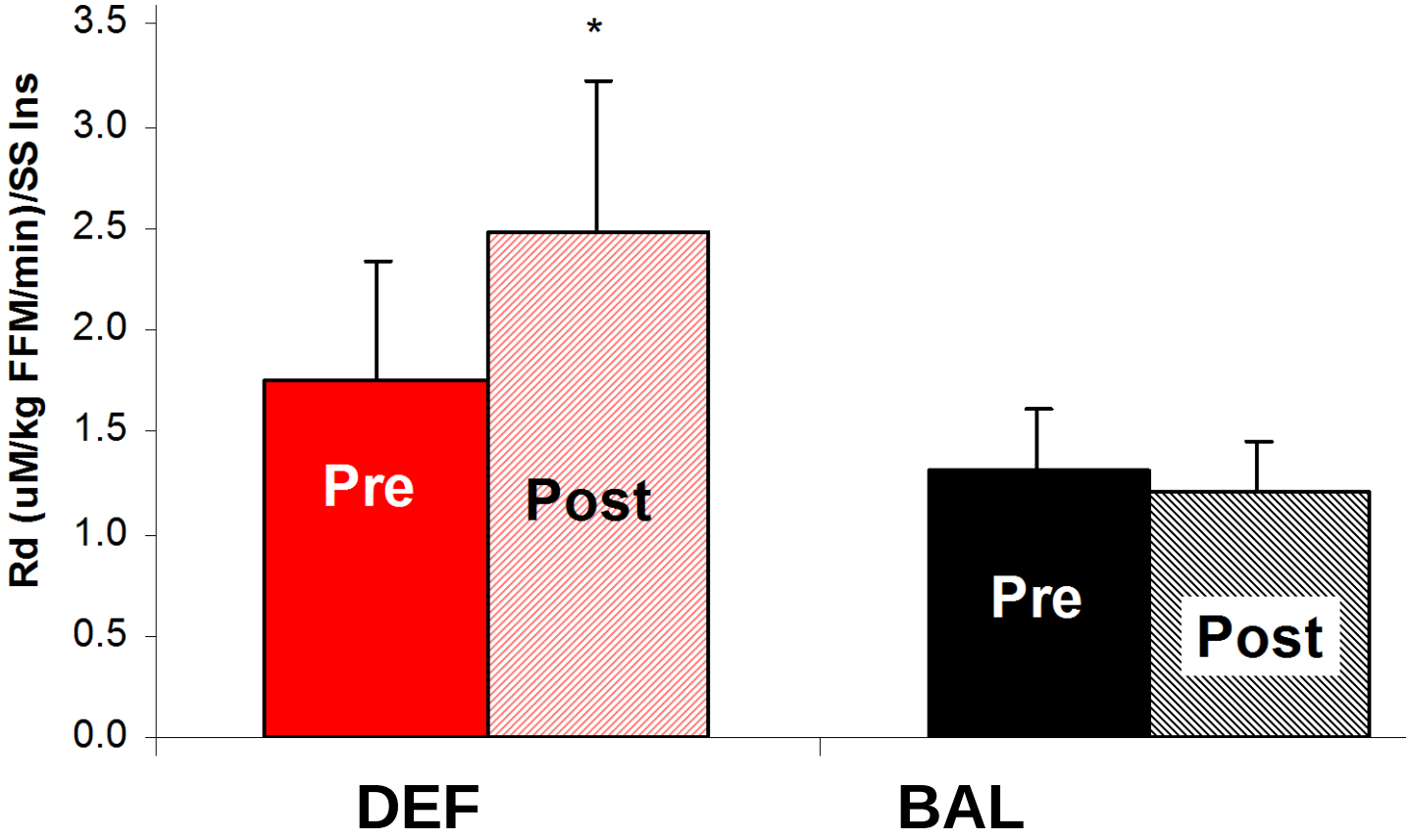
Whole-body and hepatic insulin action (CIG-SIT)



Outcomes: whole-body glucose uptake and suppression of liver glucose output



Black et al. J Appl Physiol, 2005

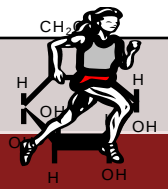


Energy balance the only difference?

CHO content of diets in 2 groups different.

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

Meal (60% CHO) immediately post-exercise

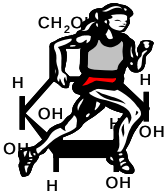


Lifestyle change

Pharmacology

exercise training

acute exercise



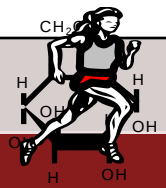
Weight loss

timing

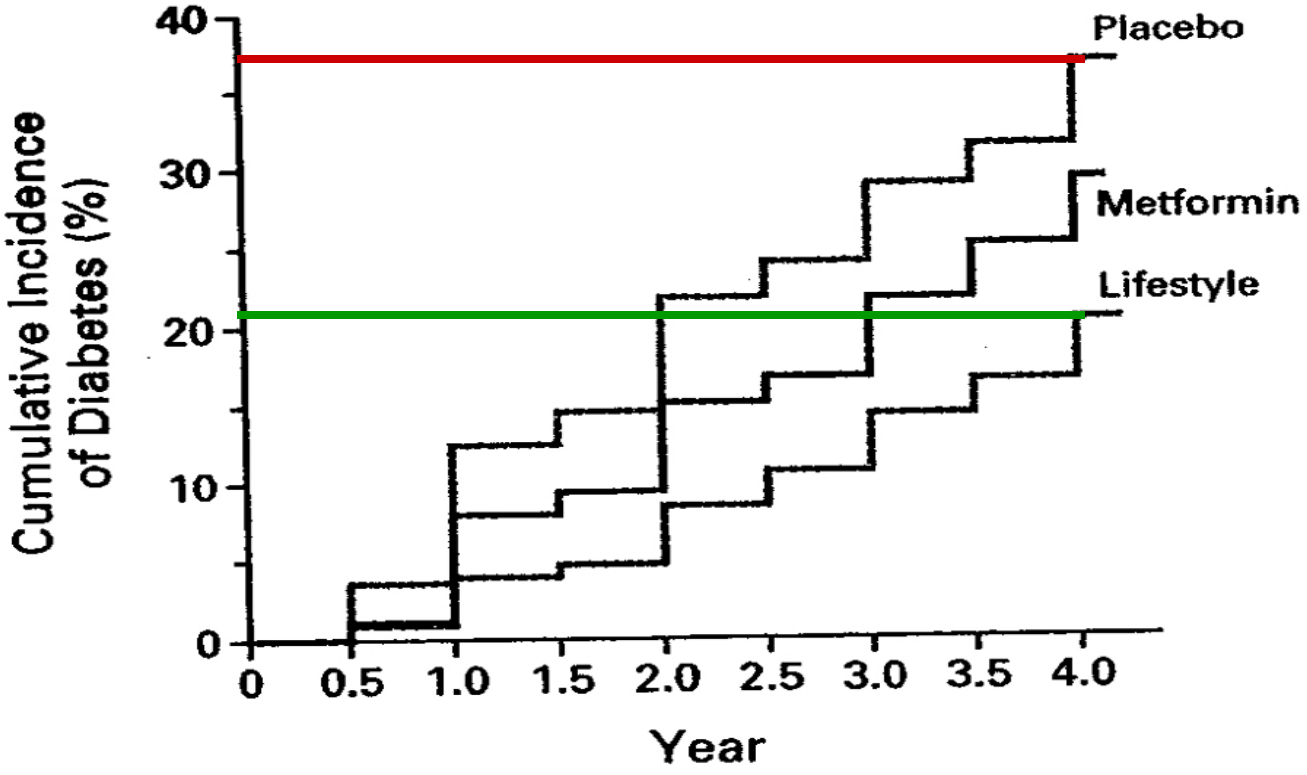
meal CHO

energy balance

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

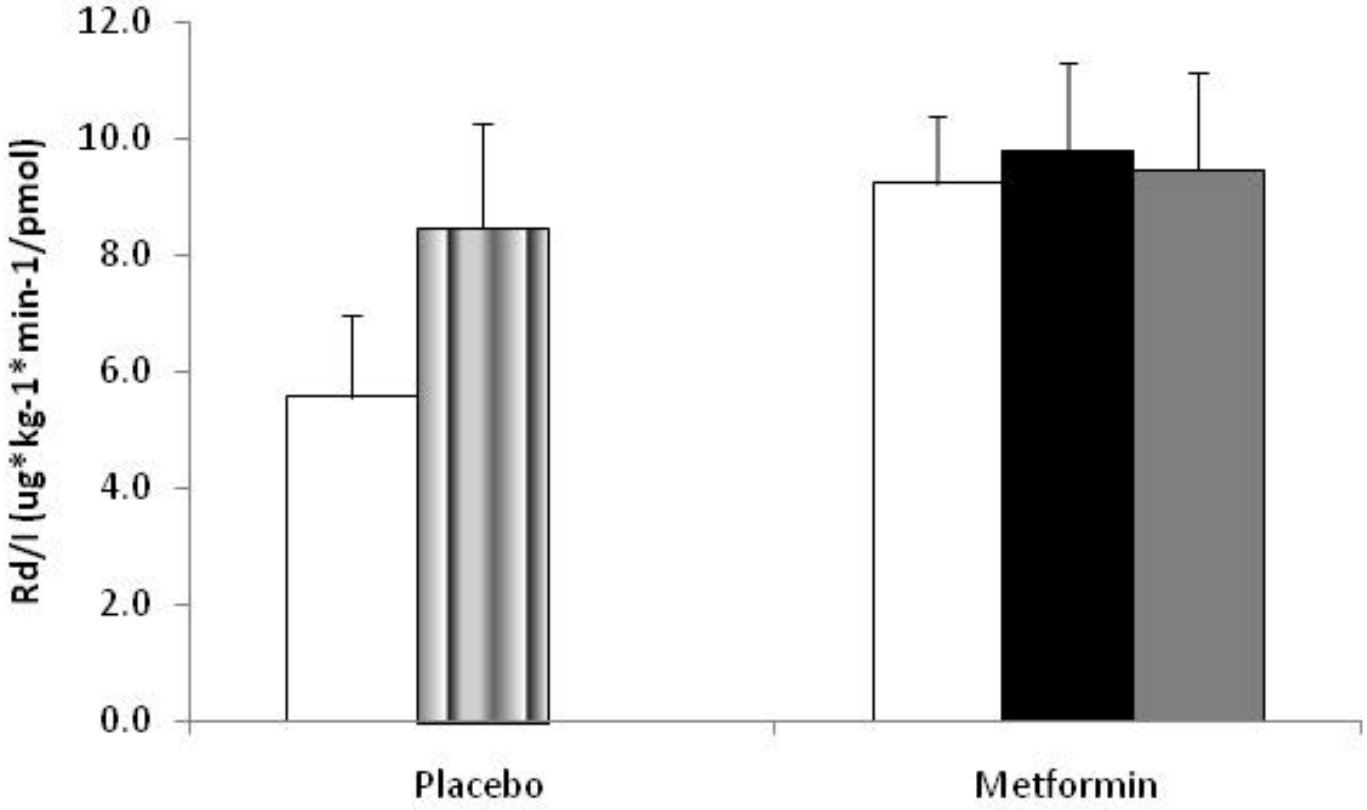
Overnight Fast	40 min rest or exercise	BIOPSY	90 min. stable isotope [6,6-2H] glucose infusion	euglycemic hyperinsulinemic clamp

Percutaneous biopsy of vastus lateralis

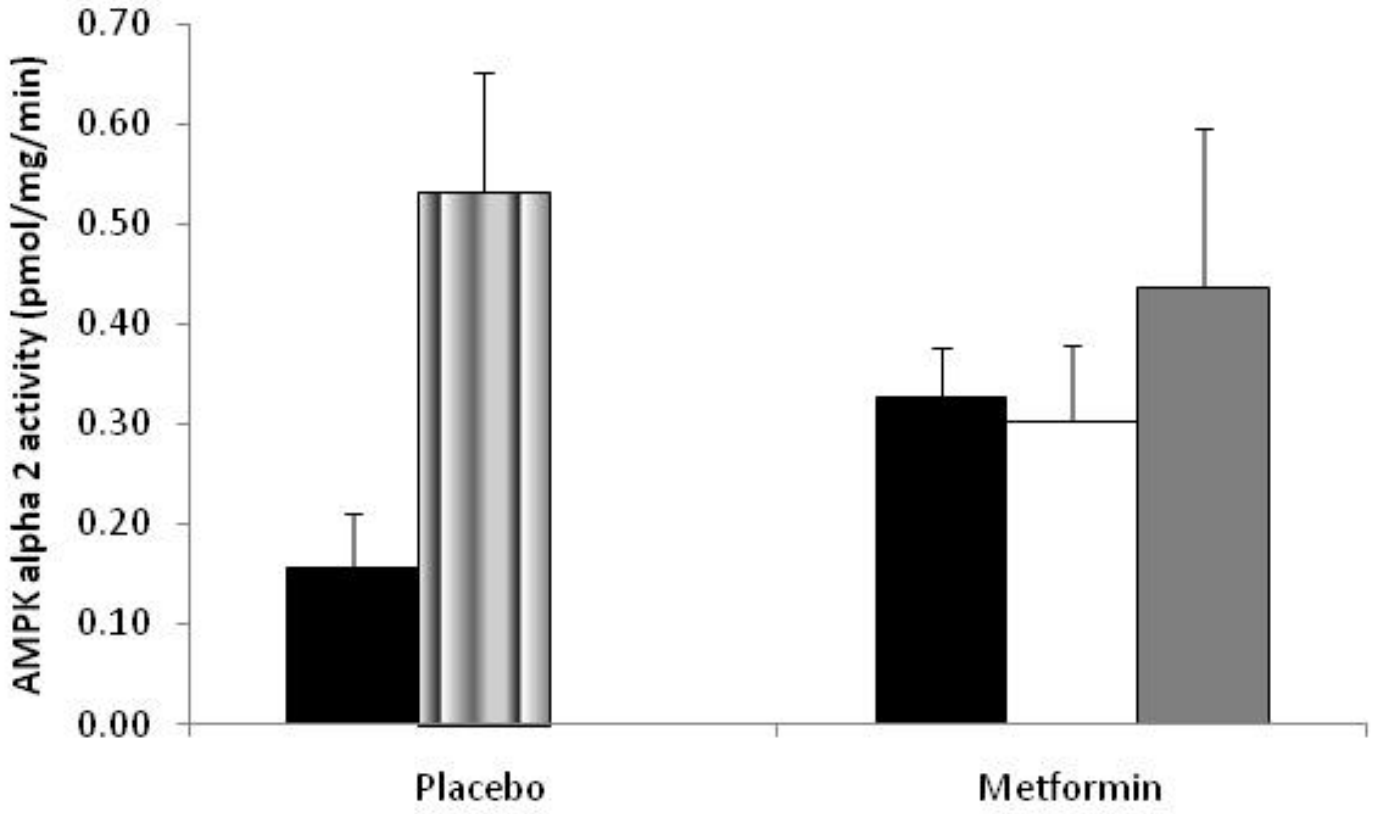
Blood sampling

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



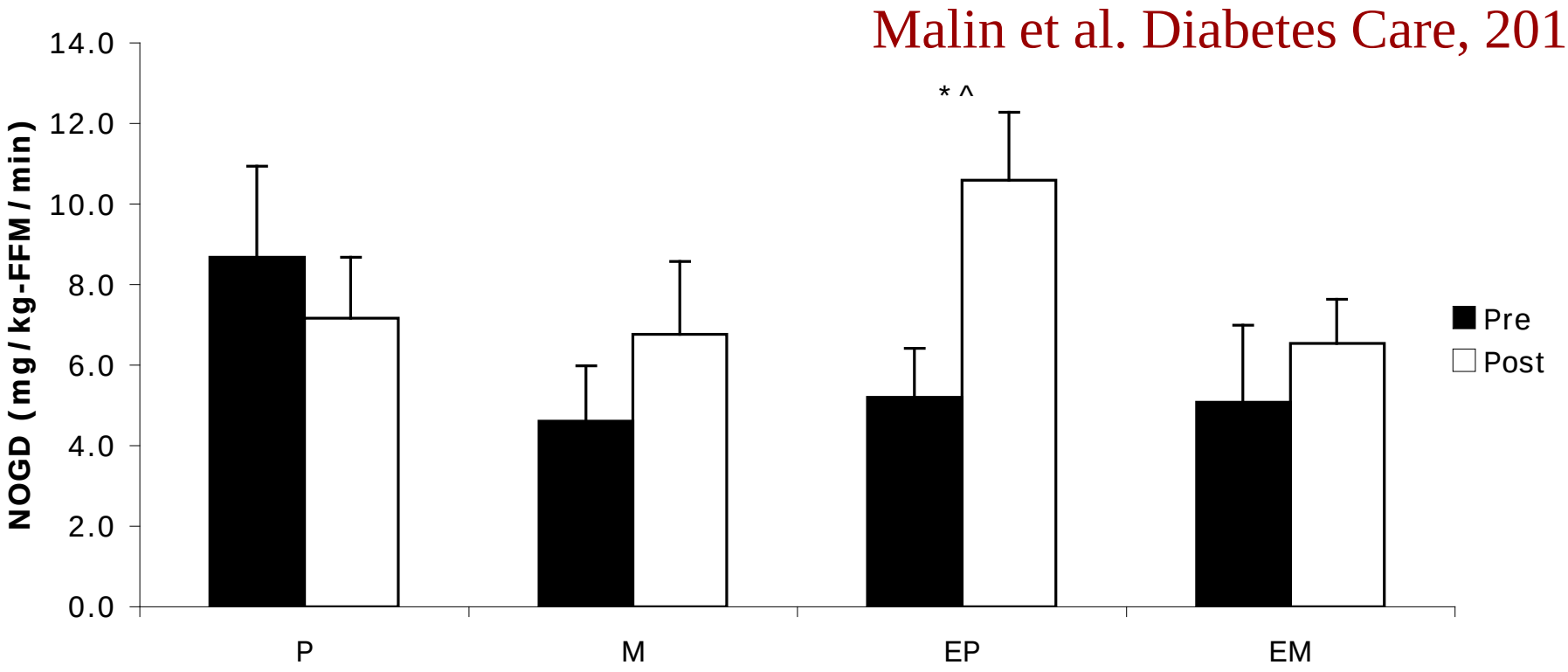
Does metformin blunt beneficial effects of training?

32 men and women with prediabetes

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

Insulin sensitivity using clamp and tracers

Malin et al. Diabetes Care, 2011



Insulin sensitivity enhanced more with exercise alone than when combined with metformin

Non glycemic outcomes

Malin et al. Obesity, 2012

SBP:

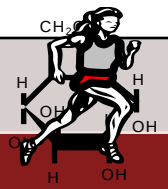
C= +6.5%, M= -7.3%, EP= -6.3%, EM= 0.0%

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%

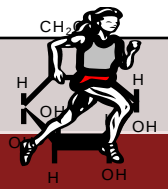


Why?

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

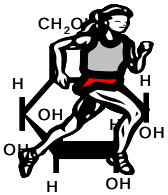


Lifestyle change

metformin

exercise training

acute exercise



Weight loss

timing

meal CHO

energy balance

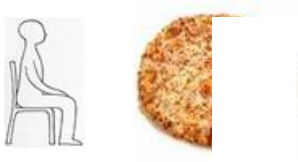
beneficial impact on metabolic health

Role of “sedentary behavior” in mediating efficacy of the exercise drug??

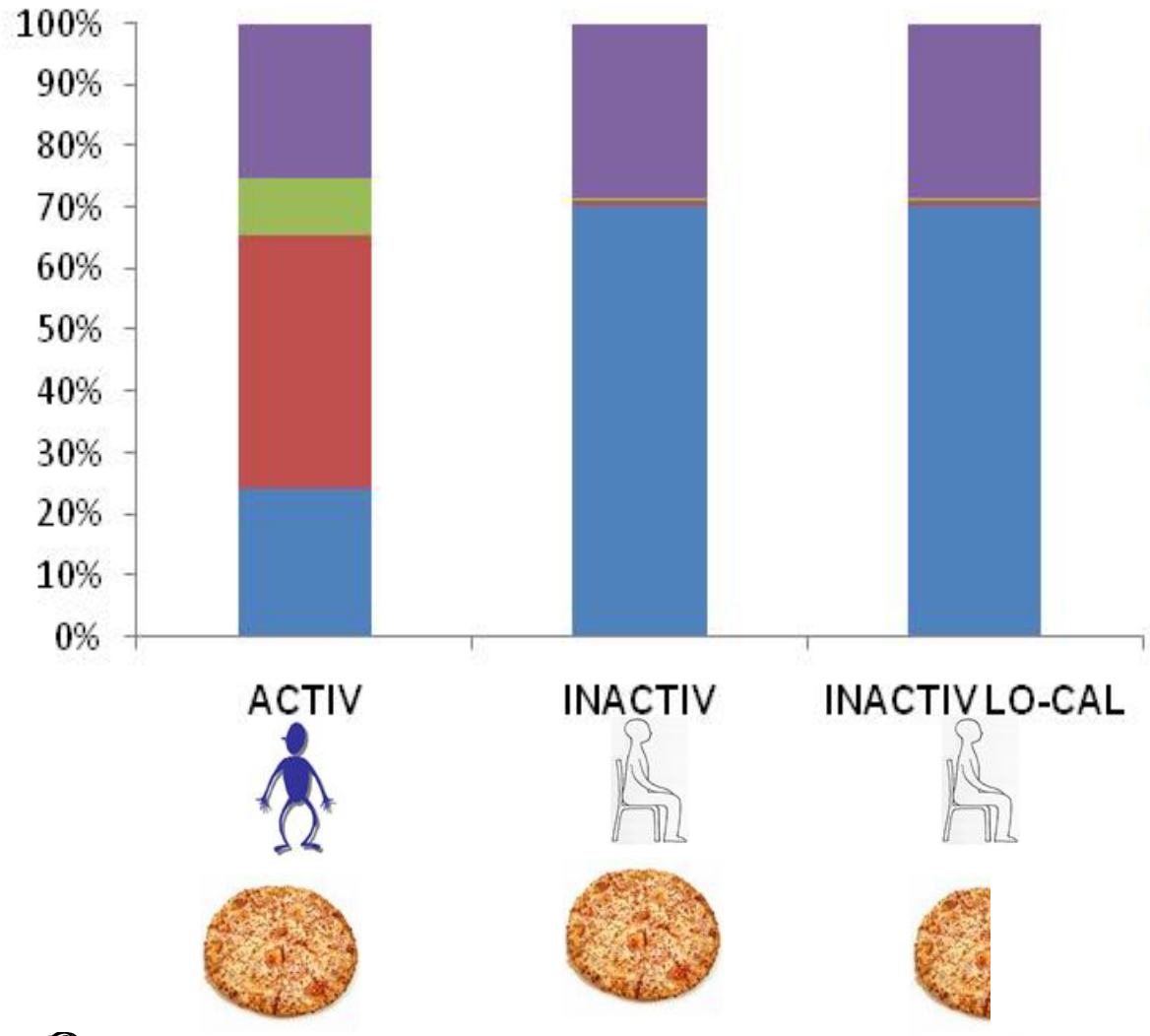
14 normally active men and women
3 conditions, balanced order

Active, energy bal (no sit 15 hr.)

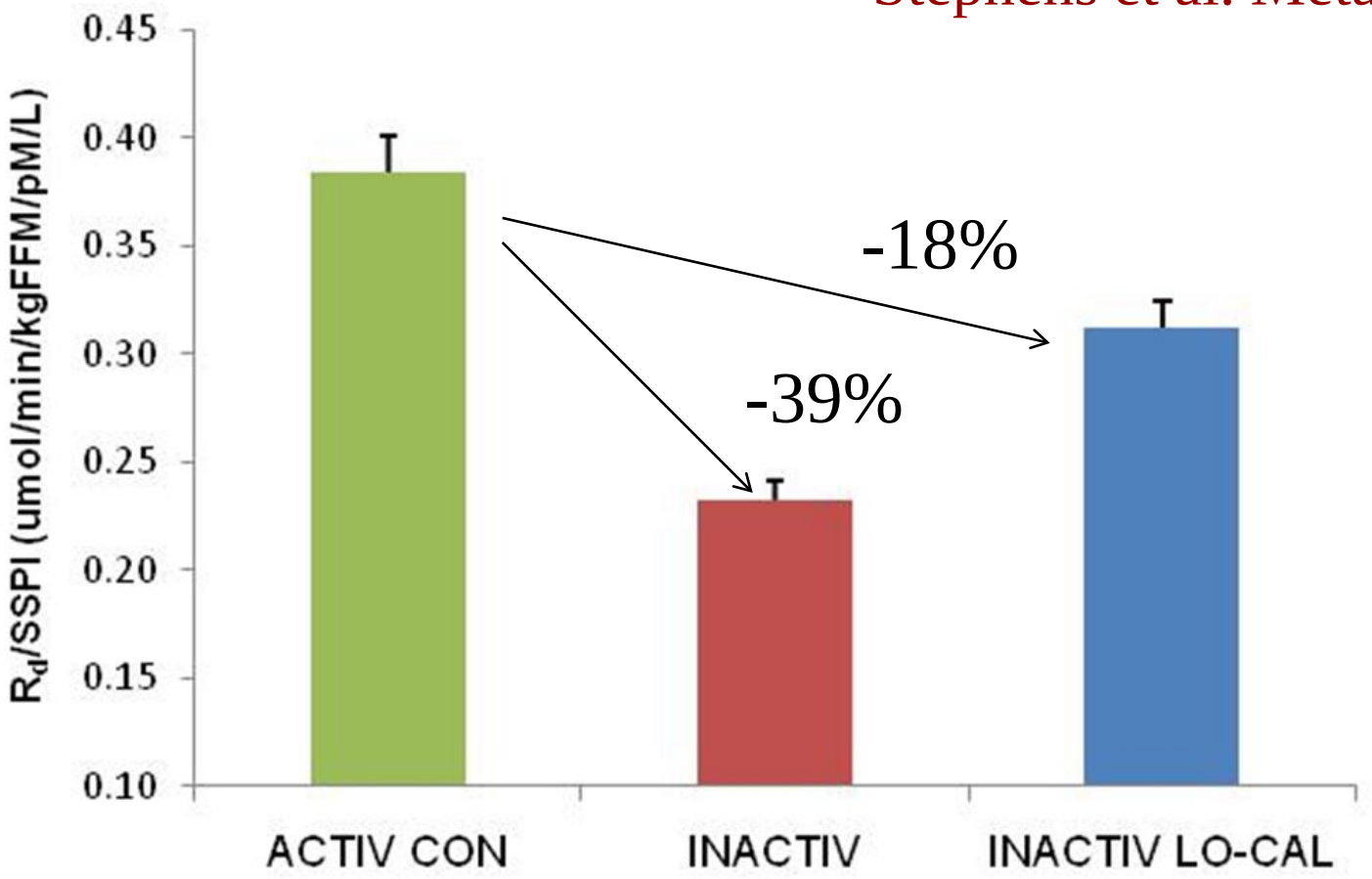
Inactive (sit 15 hr, no diet change)



Inactive, (sit 15 hr, cut kcals)


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
ACTIV
INACTIV
INACTIV LO-CAL
Sleep
Step
Stand
Sit

Stephens et al. Metabolism 2010



Kozey Keadle et al.

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)

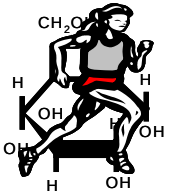
Little impact of rST alone

Lifestyle change

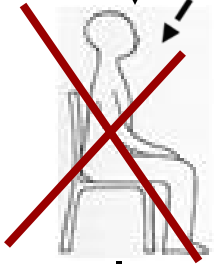
metformin

exercise training

acute exercise



Weight loss



timing

meal CHO

energy balance

beneficial impact on metabolic health

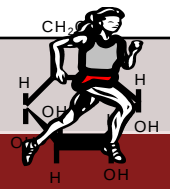
Conclusions

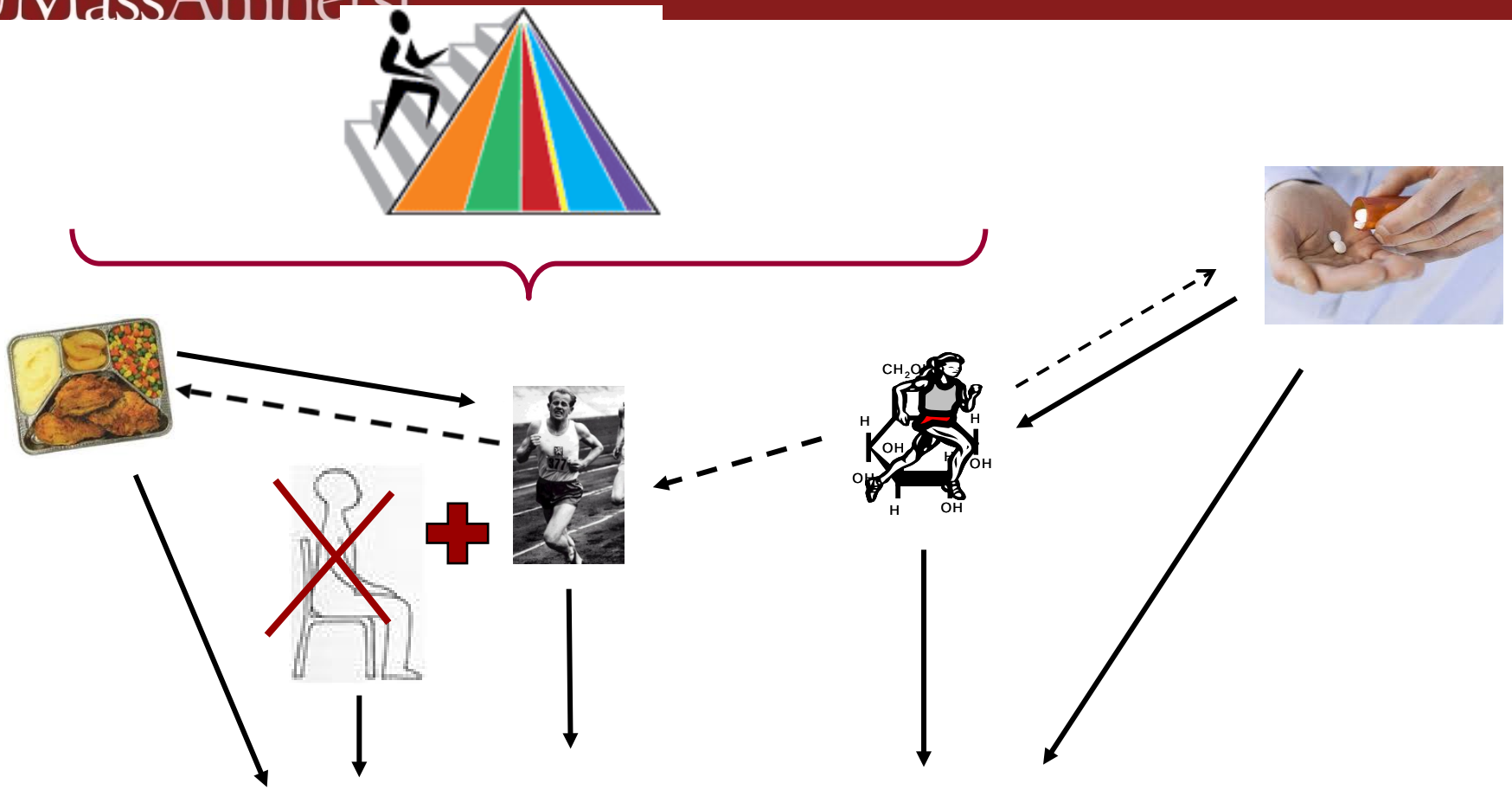
At sufficient dose, exercise/physical activity potent countermeasure

Less sedentary behavior useful but not sufficient

Interxns between exercise and nutritional context

Interactions with other meds NOT predictable





beneficial impact on metabolic health

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Kate Lyden, PhD

***NIH* 5 R56 DK081038**
American Diabetes Assoc. 7-04-JF-10
Glass Charitable Trust
Baystate/UMass CBRP
ACSM Student grants