The Role of Exercise in Maintaining Metabolic Flexibility and Control in Older People

Loretta DiPietro, PhD, MPH

Milken Institute School of Public Health
THE GEORGE WASHINGTON UNIVERSITY

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

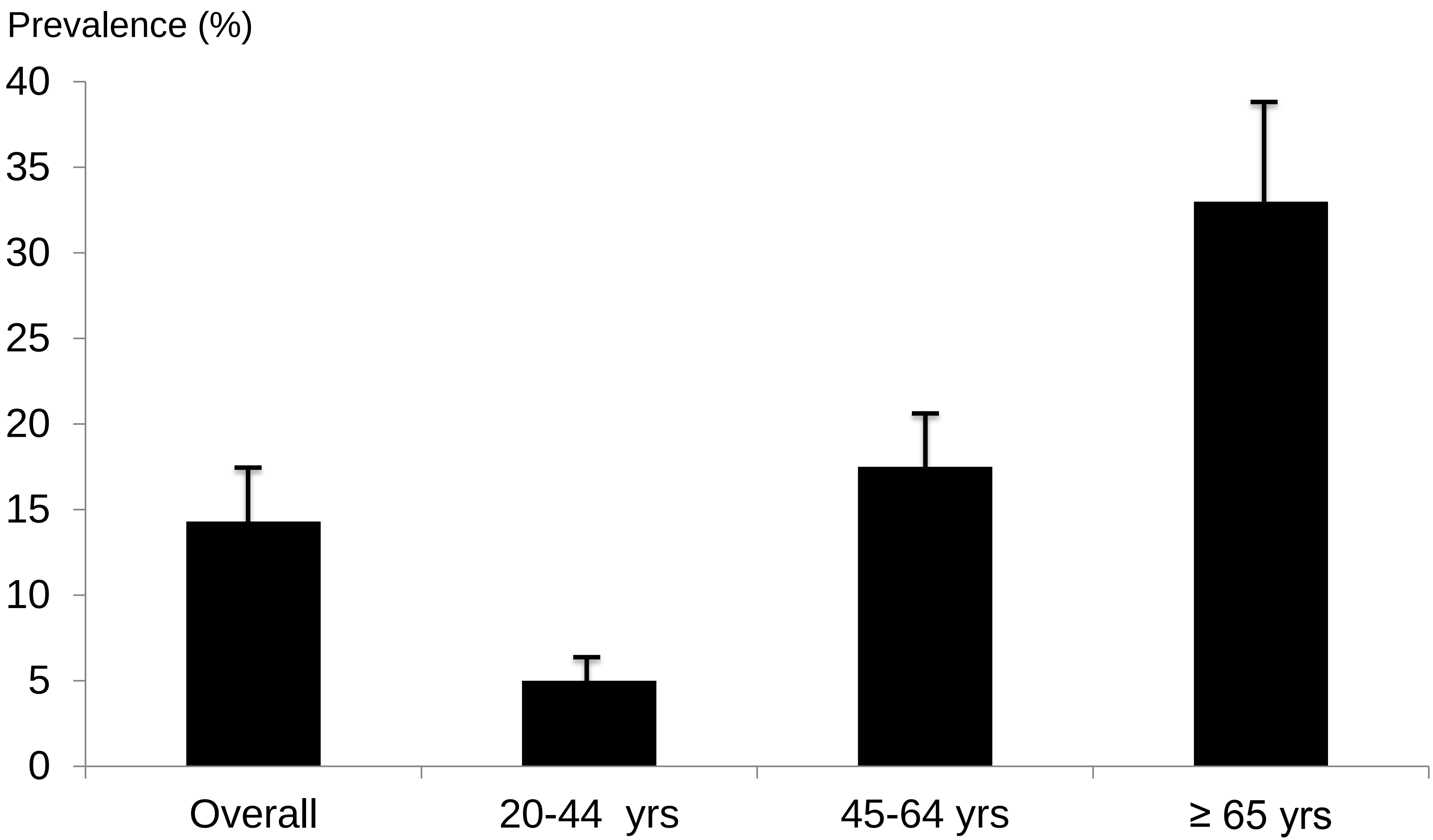
Public Health Recommendations for Older People

150 min/week of moderate-intensity activity with strengthening/balance exercise performed on 2 days/week

The Modern-Day Lifestyle

- The modern-day lifestyle is characterized by a majority of time spent sitting and reclining throughout the day;
- Older people who may spend up to 60-70% of their waking hours sitting or reclining;
- Older people may be especially vulnerable to the harmful effects of prolonged sitting due to a loss of physiologic reserve.

Prevalence of diabetes* among adults in the United States: NHANES 2011-2012 (N=2623)



*Diagnosed and undiagnosed (based on HbA1c ≥6.5%, FPG ≥126 mg·dL^{-2}, or 2h plasma glucose ≥200 mg·dL^{-2}).

Menke A, et al., *JAMA*. 2015;314:1021-1029

Background

- **O**lder people who exercise regularly appear protected from the metabolic dysregulation leading to insulin resistance and type 2 diabetes;

- **M**etabolic responsiveness to exercise training is blunted in older compared with younger people due to loss of physiologic reserve

Background

Magnitude of improvement dependent upon:

1. age of the subject;
2. initial level of impairment;
3. *absolute* intensity and volume (energy expenditure) of each training bout;
4. timing between last bout of exercise and assessment

Purpose

1) To describe the ***enduring effects*** of exercise intensity on multi-tissue insulin resistance in older people and the ***short-term effects*** of exercise of different type, volume and intensity on glucose tolerance;

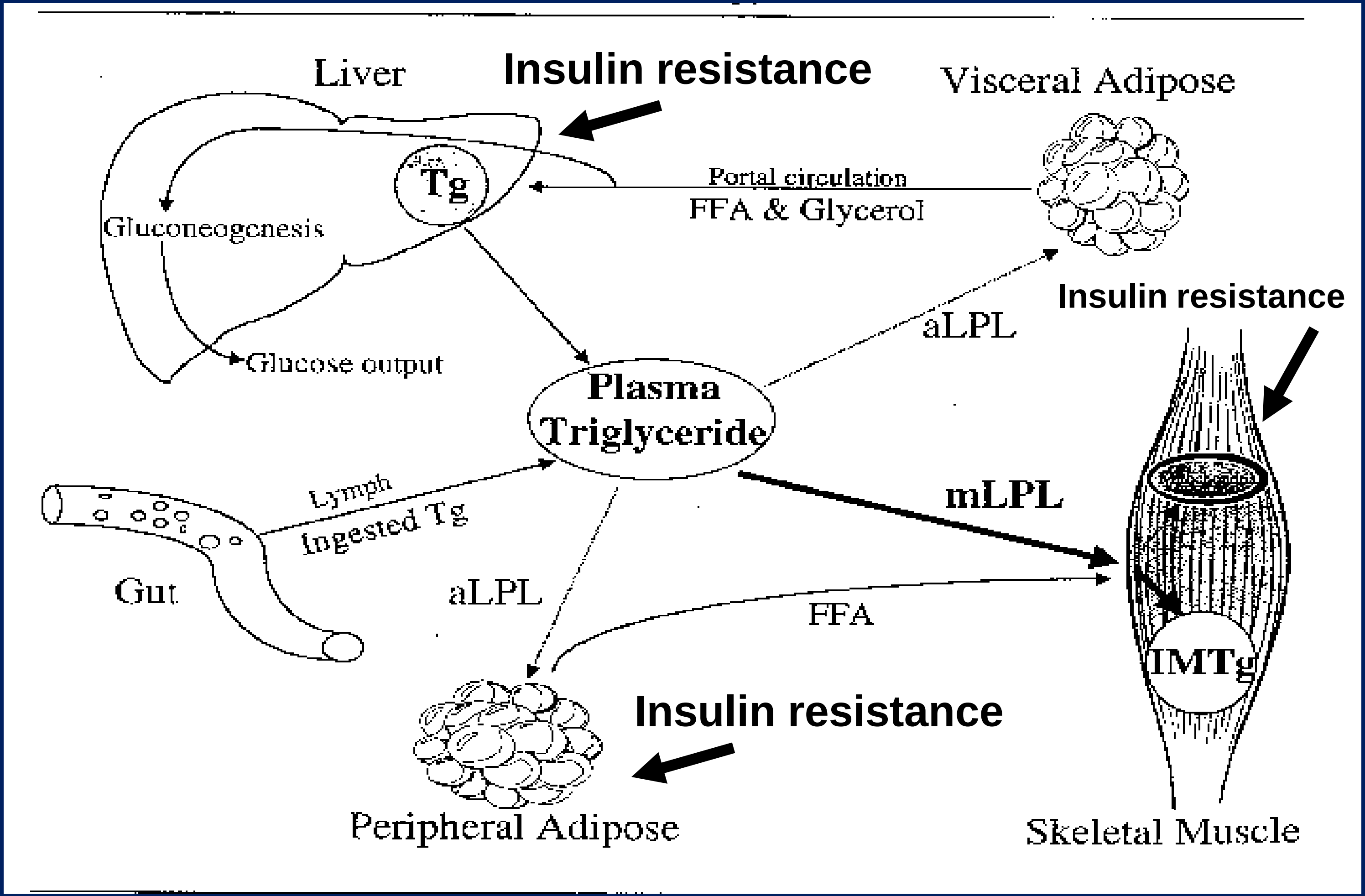
2) To describe the ***effects of timing and dosing*** of exercise on 24h and post-prandial glycemic control in older people with impaired glucose tolerance;

3) To describe preliminary findings on exercise and metabolic flexibility

The effects of exercise intensity on multi-tissue insulin resistance 72-h post-exercise.

NIH/NIA R01 AG17163

Physiological Mechanisms: multi-tissue insulin resistance



Ivy, J. *Exerc Sports Sci. Revs*, 2000.

Subjects

- Female
- ≥ 65 years
- BMI <30 $kg \cdot m^{-2}$
- Non-smokers
- No regular activity
- No HRT or glucose lowering medication

Study Protocol

Screening	Baseline	36-week Training*	Follow-up: 0-3 days	Follow-up: 4 days
Interview	CT scan	AT_H – 80%	VO_{2peak}	DXA
Physical exam	DXA	R: AT_M – 65%	OGTT	**Eugly clamp**
Anthropometry	Euglycemic clamp	RT_L	PA assessment	Muscle biopsy
PA assessment	Muscle biopsy			Bloods
OGTT	Bloods			
VO_{2peak}				

*** Training period includes a 4-6 week "hardening" period. All groups train 4 days/week for 60-90 mins. Assuming a VO_{2peak} of ~1.40 $L \cdot min^{-1}$ for a 68 kg woman, it requires about 55 min at 80% or 65 min at 65% to expend 300 kcal (1 L O_2=5 kcal).**

Exercise Training Protocols

4 days per week for 9 months

R

Low	Moderate	Higher
•Strengthening	•65% VO2peak	•80% VO2peak
•Stretching	•Aerobic	•Aerobic
•45 min	•~65 min*	•~55 min*
	•300 kcal	•300 kcal

*Based on VO_{2peak} of ~1.4 $L \cdot min^{-1}$ for a 68 kg older woman.

Euglycemic – Hyperinsulinemic Clamp Protocol

Time of day

0700 to 1000 | 1000 to 1400

Basal glucose kinetics

2-step Euglycemic-Hyperinsulinemic clamp

10 mU·m^{-2}·min^{-1} **40 mU·m^{-2}·min^{-1}**

0 -60 -90 -120 0 30 60 90 120 150 180 210 240

Catheters in

Baseline bloods

Infusion of 6,6^{2}H -glucose and $^2H_5$ -glycerol

Biopsy

Blood sampling for 6,6-^{2}H and $^2H_5$

Indirect calorimetry

Infusion of insulin/ glucose

Sampling q5 glucose and q30 insulin, FFA

Blood sampling for 6,6-^{2}H and $^2H_5$

Indirect calorimetry

Blood sampling for 6,6-^{2}H and $^2H_5$

Indirect calorimetry

Performed in the metabolic unit of the GCRC at Yale-New Haven Hospital.

Table 1. – General characteristics of the study population before and after training

	Thera-band (n=7)		Moderate-intensity (n=9)		Higher-intensity (n=9)	
	Baseline	**9-mths**	**Baseline**	**9-mths**	**Baseline**	**9-mths**
Age (y)	75±5		73±3		72±3	
VO_{2peak} (ml·(kg·min)$^{-1}$	18.3±4.2	18.7±2.6	21.2±3.4	21.1±3.0	21.4±3.9	21.0.±4.2
Activity* (kcal·wk^{-1})	4433±1075	4724±1721	5714±2192	6426±1768	5414±3066	6726±3387

Values are means±SD. * Self-reported physical activity from the Yale Physical Activity Survey and adjusted for seasonal variation.

Di Pietro, et al., *J Appl Physiol*. 2006;100:142-149.

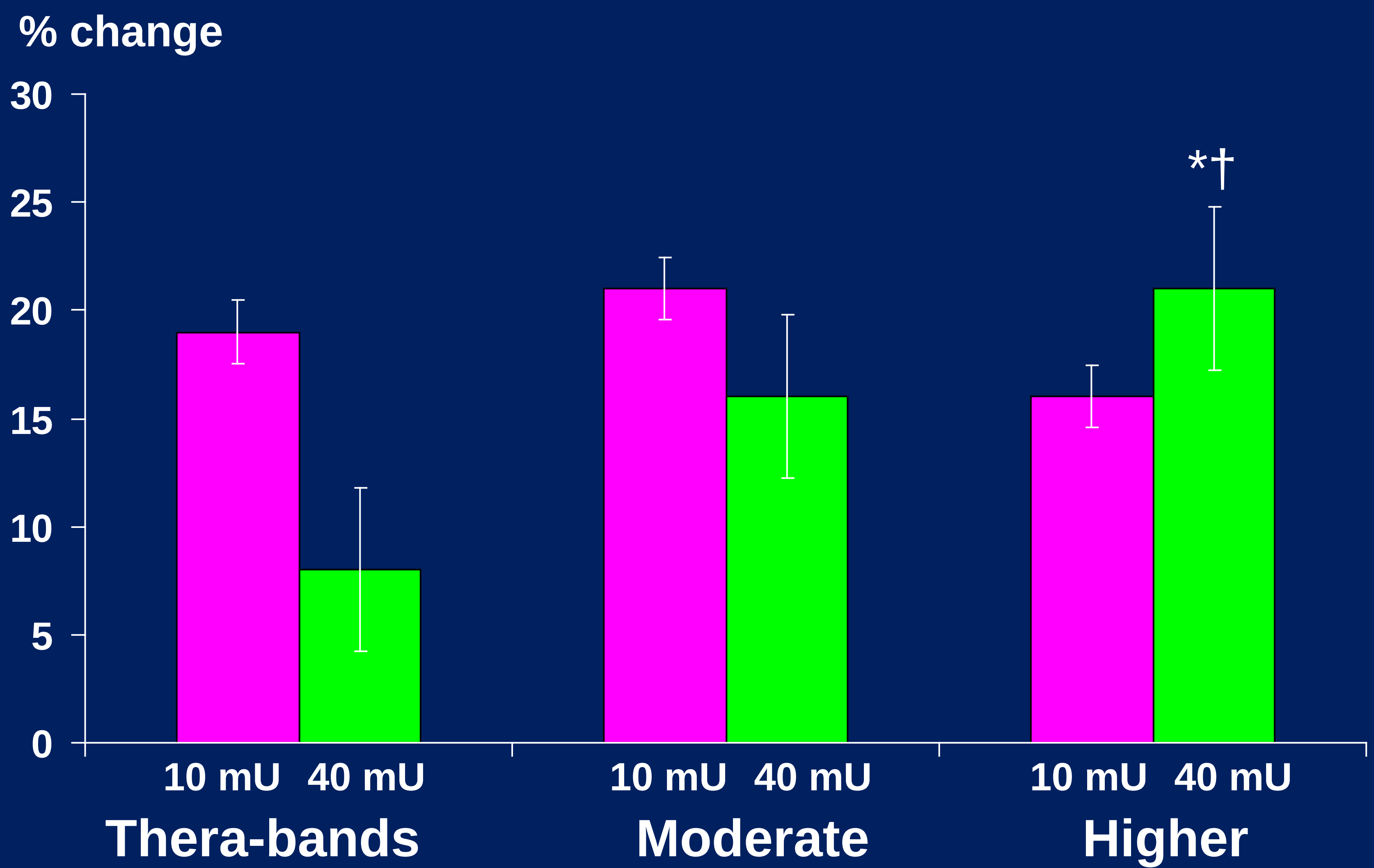
Table 2. – Anthropometric characteristics of the study population before and after training.

	Thera-band (n=7)		Moderate-intensity (n=9)		Higher-intensity (n=9)	
	Baseline	**9-mths**	**Baseline**	**9-mths**	**Baseline**	**9-mths**
BMI ($kg \cdot m^{-2}$)	27.7±4.7	27.3±4.7	28.0±4.5	27.6±4.5	26.3±3.0	26.4±3.6
Lean Mass (kg)*	38.7±6.8	39.4±7.0	39.6±7.2	39.3±8.1	41.9±8.1	42.3±8.4
Body fat (%)*	38±5	38±5	38±6	37±6	38±6	38±6
Abdominal cir (cm)	95.9±13.3	93.9±14.0	96.0±14.7	94.5±13.8	99.1±13.8	96.4±13.2

*Based on DXA. Values are means±SD.

Di Pietro, et al., *J Appl Physiol*. 2006;100:142-149.

Training-related improvements (%Δ) in the glucose utilization rate at low and high dose insulin



*$p<0.05$ within group; † $p<0.05$ compared with C_{TB}.

DiPietro, et al. *JAP*, 2006

Table 3b. - Metabolic characteristics of the study population during the euglycemic-hyperinsulinemic clamp, before and after training.

	Thera-band (n=7)		Moderate-intensity (n=9)		Higher-intensity (n=9)	
	Baseline	**9-months**	**Baseline**	**9-months**	**Baseline**	**9-months**
M-value at 10mU (mg·(kg lean· min)$^{-1}$)	2.1±1.56	2.5±2.08	1.4±1.21	1.7±1.53	1.9±1.22	2.2±1.22
M-value at 40mU (mg·(kg lean· min)$^{-1}$)	7.5±2.08	8.1±3.38	6.2±3.31	7.1±2.73	7.5±3.62	9.0±3.60*
M_{40}/I (μU·mL^{-1})	0.09±0.03	0.08±0.03	0.08±0.06	0.07±0.03	0.08±0.03	0.10±0.03*†
Basal HGP (mg·(kg·min)$^{-1}$)	1.70±0.31	1.72±0.26	1.89±0.30	1.63±0.27*	1.65±0.30	1.73±0.27
HGP at 10mU (mg·(kg·min)$^{-1}$)	0.57±0.70	0.23±0.81	0.82±0.42	0.41±0.30*	0.37±0.69	0.27±0.48

HGP=Hepatic glucose production; M-value=whole-body glucose metabolism rate and both low (10mU·m^{-2}·min^{-1}) or high (40mU·m^{-2}·min^{-1}). M-value at 40 mU/plasma insulin concentrations over the last 30 min of the clamp. * Within-group improvement, P<0.02. †P<0.05 vs T_M or C_{TB} group.

Di Pietro, et al., *J Appl Physiol*. 2006;100:142-149.

Table 4. –Glycerol turnover* during hyperinsulinemia before and after training

	Thera-band (n=7)		Moderate Intensity (n=9)		Higher Intensity (n=9)	
	Baseline	9-months	Baseline	9-months	Baseline	9-months
Basal R_a/R_d **($mg \cdot (kg \cdot min)^{-1}$)**	0.29±0.05	0.26±0.08	0.28±0.09	0.26±0.03	0.29±0.12	0.27±0.06
R_a/R_d 10 mU **$(mg \cdot (kg \cdot min)^{-1}$**	0.16±0.05	0.13±0.05	0.15±0.06	0.14±0.03	0.19±0.09	0.12±0.03*†
R_a/R_d 40 mU **$(mg \cdot (kg \cdot min)^{-1}$**	0.14±0.05	0.10±0.05	0.12±0.03	0.11±0.03	0.17±0.09	0.11±0.03

* Data obtained during steady state conditions, in which the R_a (rate of appearance) is equal to the R_d (rate of disappearance). *within-group improvement P<0.05; † P<0.05 compared to T_M.

Di Pietro, et al., *J Appl Physiol*. 2006;100:142-149.

Summary

- No change in $VO2_{peak}$ or in body composition;
- Improved glucose utilization at the higher insulin dose that was statistically significant only in the T_H (21%; $p<0.02$) compared with the T_M (16%) and C_{TB} (8%) groups *and was evident 72 h after exercise*;
- Improved M/I index in T_H group (25%; $p<0.05$);
- Improved glycerol turnover (from 38% to 55%; $p<0.05$) in the T_H group at the low insulin dose.

Transient Improvements in Glucose Tolerance at 48h Post-Exercise: the Roles of Volume and Intensity

Low-volume resistance
vs.
High-volume/moderate-intensity aerobic

NIH/NIA R01 AG17163

Study Protocol

Screening	Baseline	36-week Training*	Follow-up	
			0-3 days	4 days
Interview	CT scan	AT_H – 80%	VO_{2peak}	DXA
Physical exam	DXA	R	**OGTT**	Eugly clamp
Anthropometry	Euglycemic clamp	AT_M – 65%	PA assessment	Muscle biopsy
PA assessment	Muscle biopsy	Placebo		Bloods
OGTT	Bloods			
VO_{2peak}				

*** Training period includes a 4-6 week "hardening" period. All groups train 4 days/week for 60-90 mins. Assuming a VO_{2peak} of ~1.40 $L \cdot min^{-1}$ for a 68 kg woman, it requires about 55 min at 85% or 65 min at 65% to expend 300 kcal (1 L O_2=5 kcal).**

DiPietro, et al., *JPAH* 2008

Figure 8. – Progressive improvements in glucose and insulin responses to an OGTT with lower-intensity exercise training in older women.

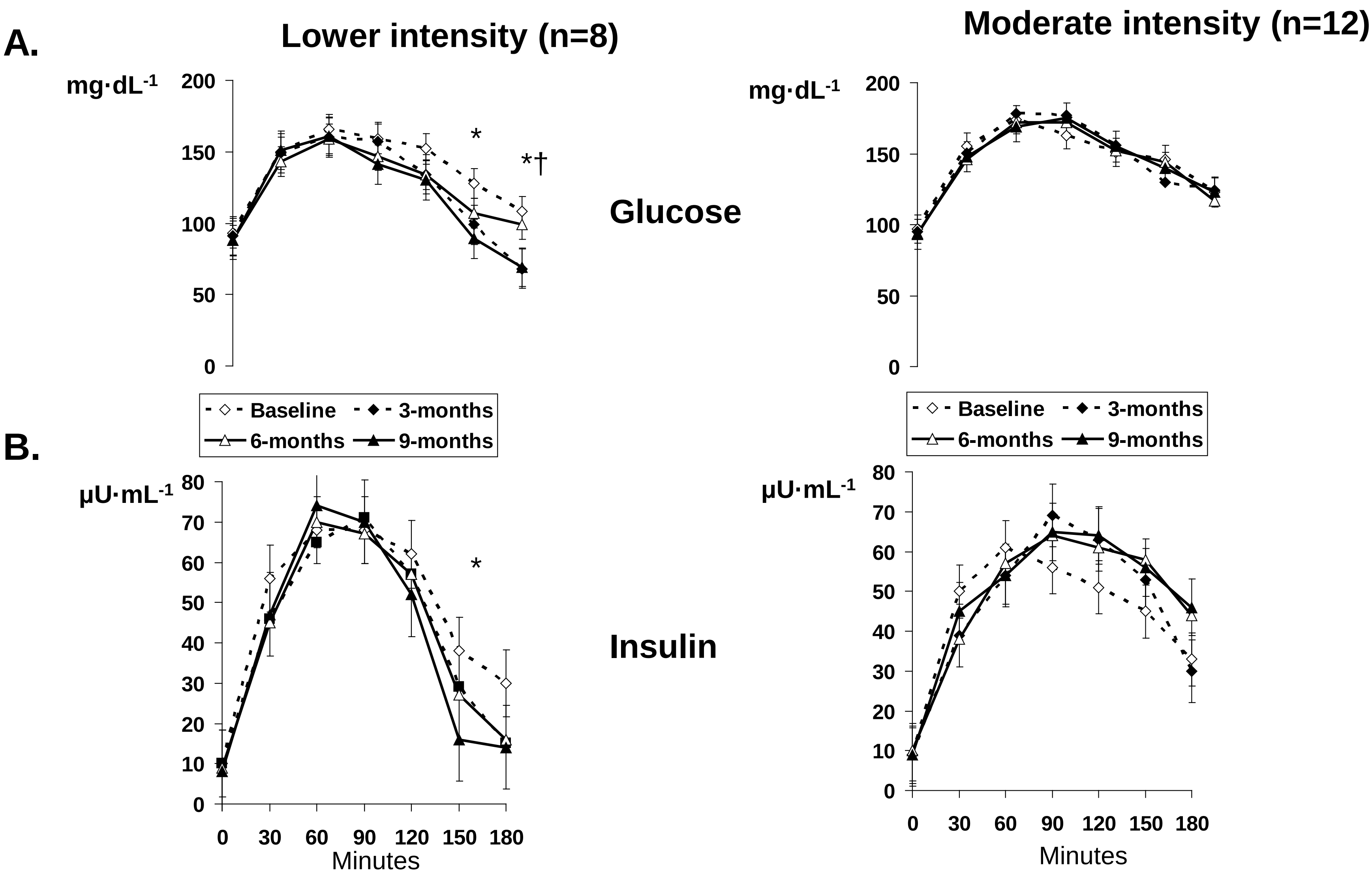
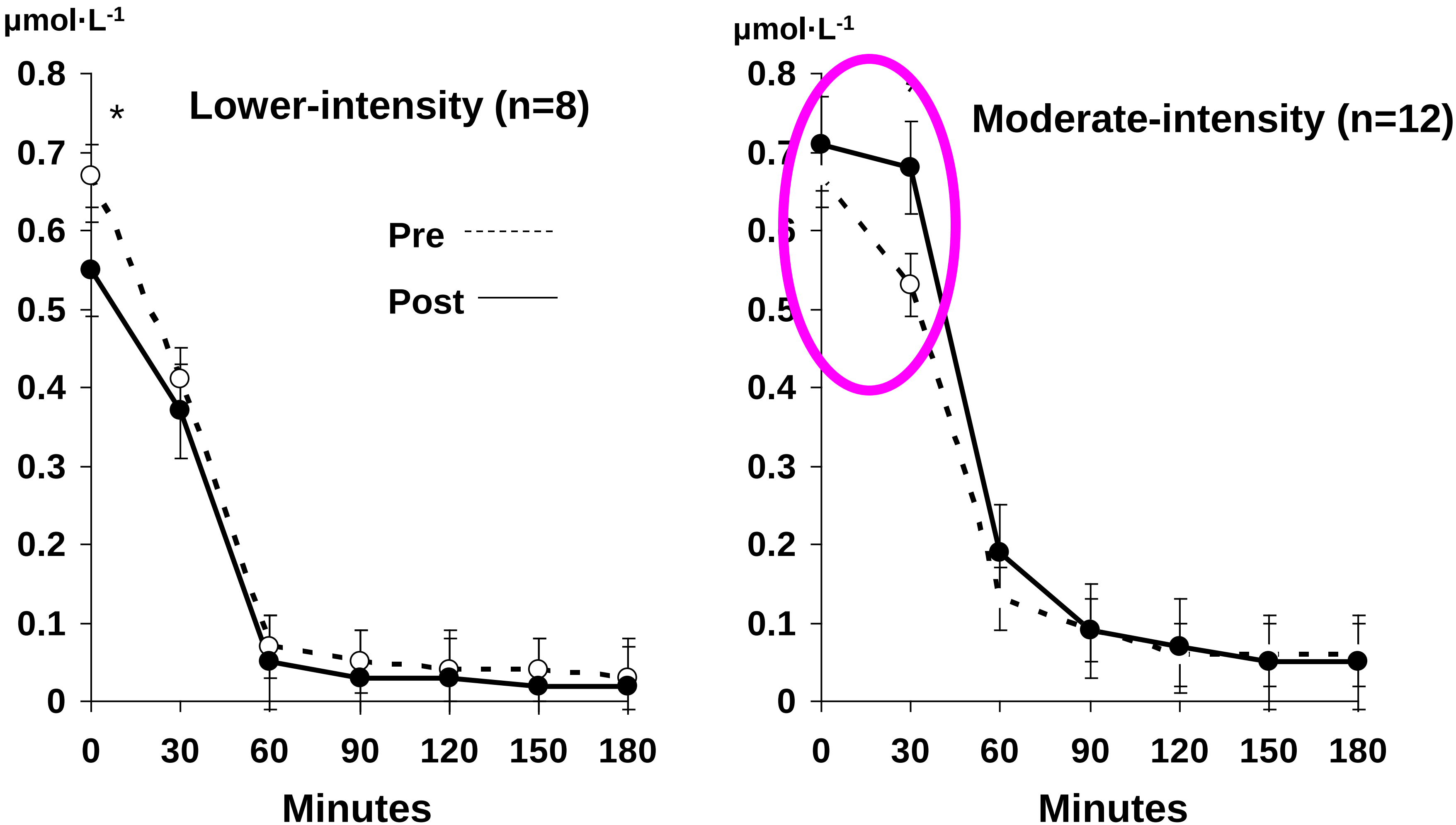


Figure 10. – Improvements in insulin suppression of plasma FFA concentrations with lower- but not moderate-intensity training.



DiPietro, et al., *JPAH* 2008

Summary

- We observed a greater *short-term* (i.e., 48-h) effectiveness of lower-intensity resistance exercise compared with high volume/moderate-intensity aerobic training on improvements in glucose tolerance

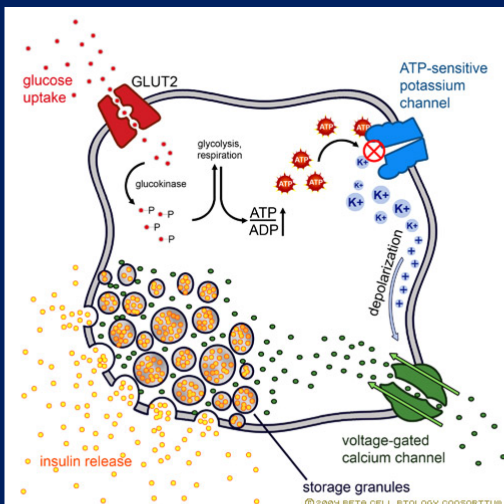
- This may be explained in part by the positive changes in muscle quality resulting from resistance training that are not hindered by a persistent stress response.

- The higher circulating levels of FFA after a large volume of moderate-intensity aerobic exercise may have temporarily interfered with insulin action in the liver and muscle, thus altering the **metabolic benefit-to-stress ratio** of the exercise among women in the AT_M group.

Exercise Timing and Dosing

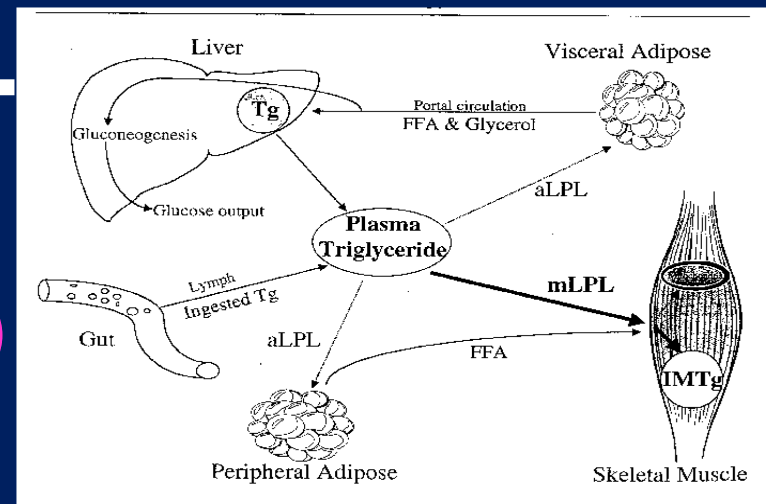
R_x vs R_x R_x R_x

Metabolic Control in Aging

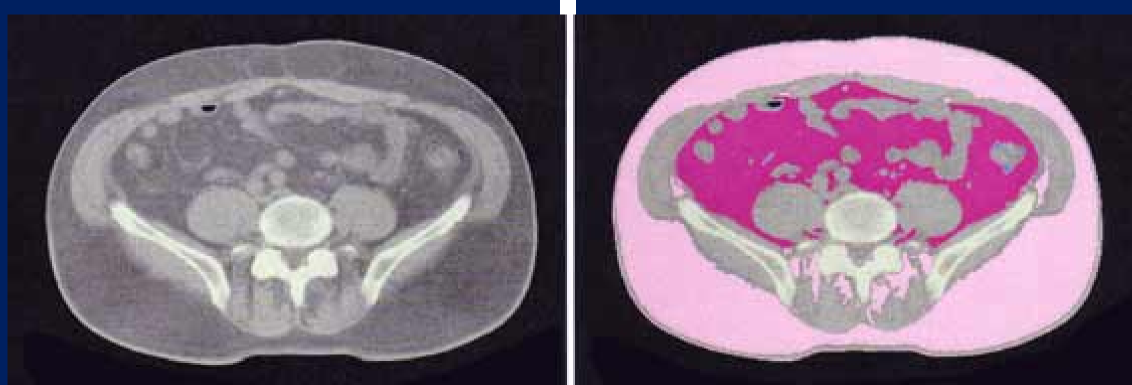


Loss of β-cell function

Impaired glycemic control



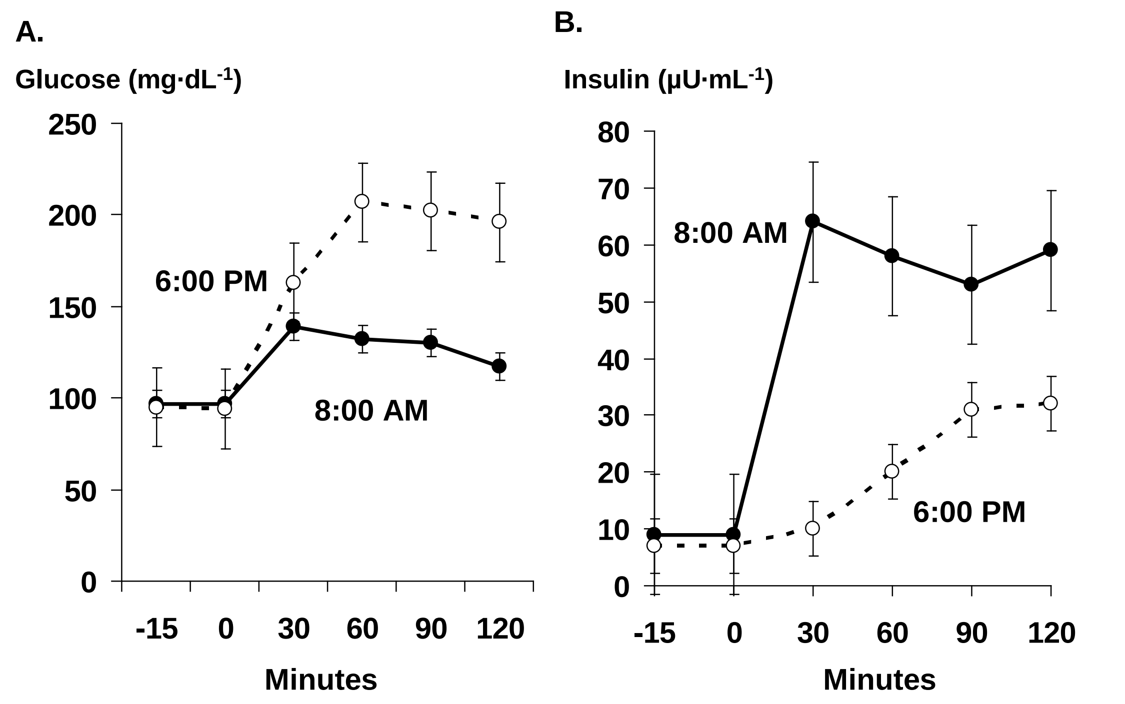
Disuse-related multi-tissue IR



Excess visceral adiposity

Diurnal Variation in Insulin Secretion in Older People

Figure 4.- Diurnal variation in (A) glucose and (B) insulin responses to an OGTT in older people with normal glucose tolerance (N=4).



DiPietro, (unpublished)

The Role of Exercise

- Both insulin and muscle contractions (exercise) stimulate the translocation of GLUT-4 transporter proteins to the surface of the plasma membrane in muscle;
- The effects of these processes are to some degree additive;
- Exercise enhances skeletal muscle capillary perfusion, which increases the surface area for both glucose and insulin interaction with muscle;
- **Thus, muscle contractions *per se* can stimulate insulin action independent of endogenous insulin secretion**

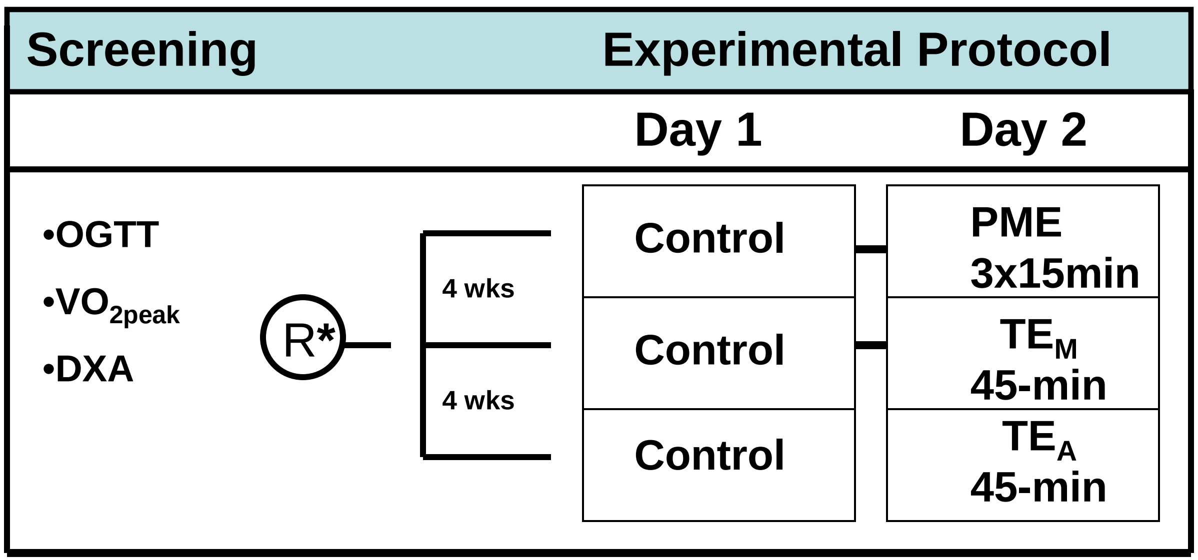
Timing and Dose of Exercise

Given the loss of β-cell function with age and the consequent vulnerability of older people to post-prandial hyperglycemia *–especially later in the day--* it seems reasonable that 15-min of exercise performed <u>after each meal</u> (during the period of absorption) would have a greater benefit to post-prandial, as well as to 24-h glucose control than would a single large bout (45 min) of exercise performed before meals

NIH/NIA R21 AG031550

Low-intensity (3 METs) post-meal walking and 24-h glycemic control in older people with IGT

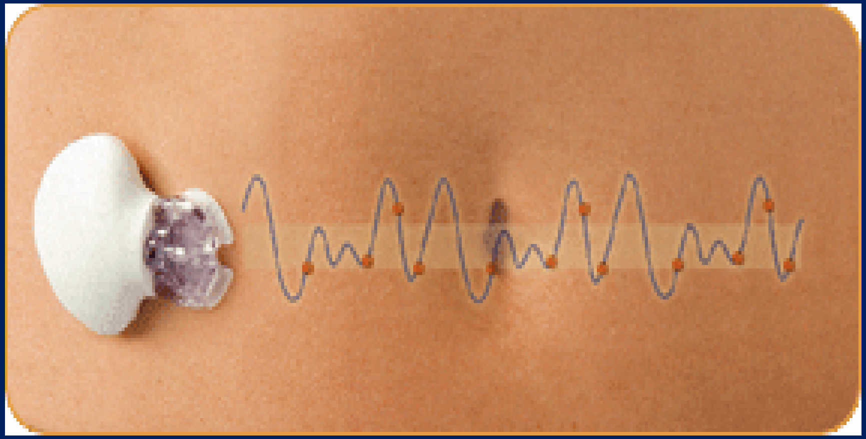
Overall Study Protocol



OGTT=oral glucose tolerance test; VO_{2peak}=peak aerobic capacity; DXA=dual energy x-ray absorptiometry; * Experimental conditions randomly-ordered and spaced 4 weeks apart.

The Continuous Glucose Monitoring System (CGMS)*

- Measures interstitial glucose levels up to 288 times per day for up to 72 h;
- Can study glycemic responses to meals and exercise <u>continuously</u> under *real-life* conditions;
- Can provide details of the direction, magnitude, duration, and frequency of glycemic excursions over 24 h;

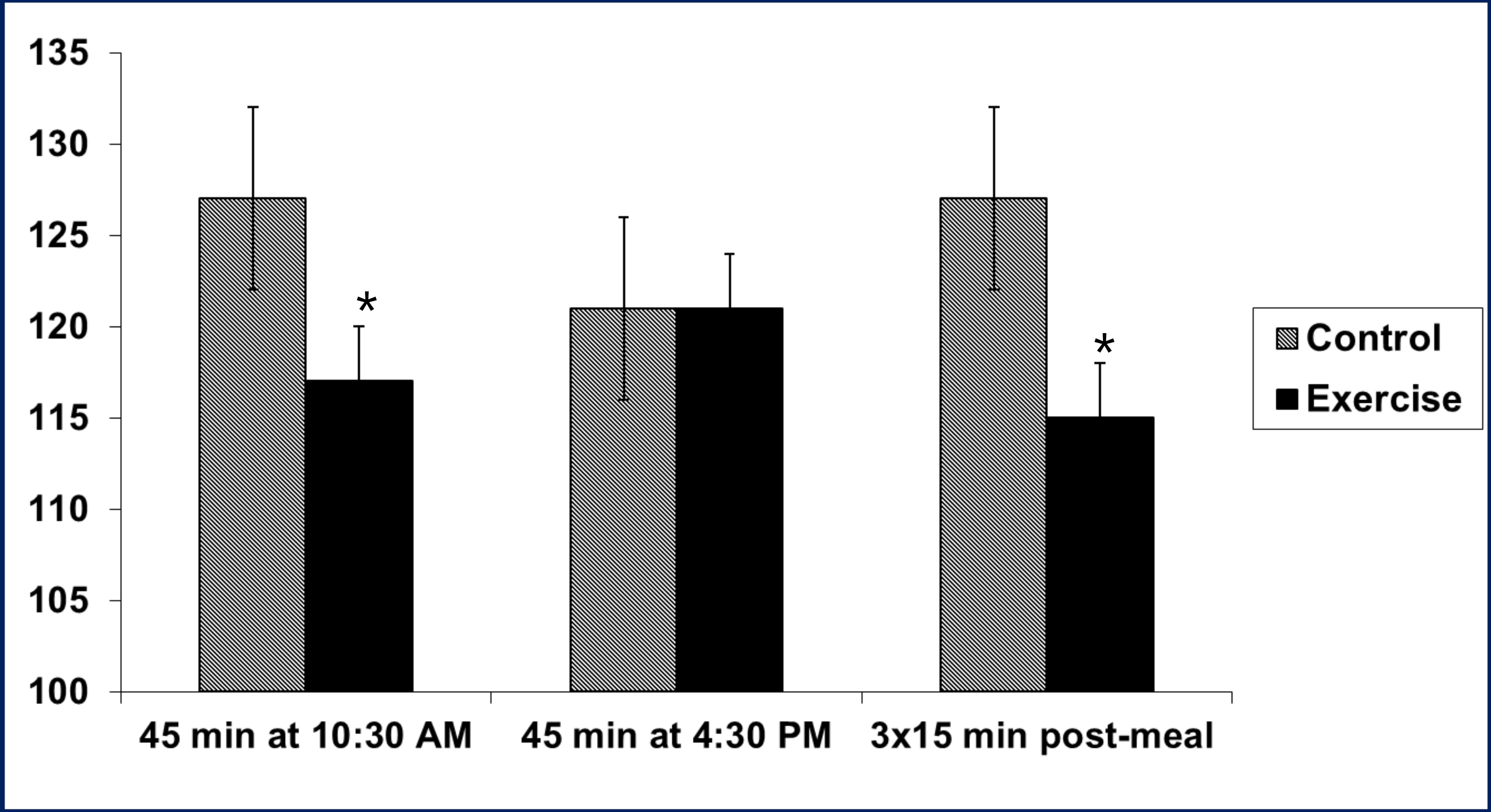


*CGMS *i*-Pro; Medtronics, Northridge, CA

Whole-room Calorimeter

24h glucose levels between the control and exercise day by exercise protocol

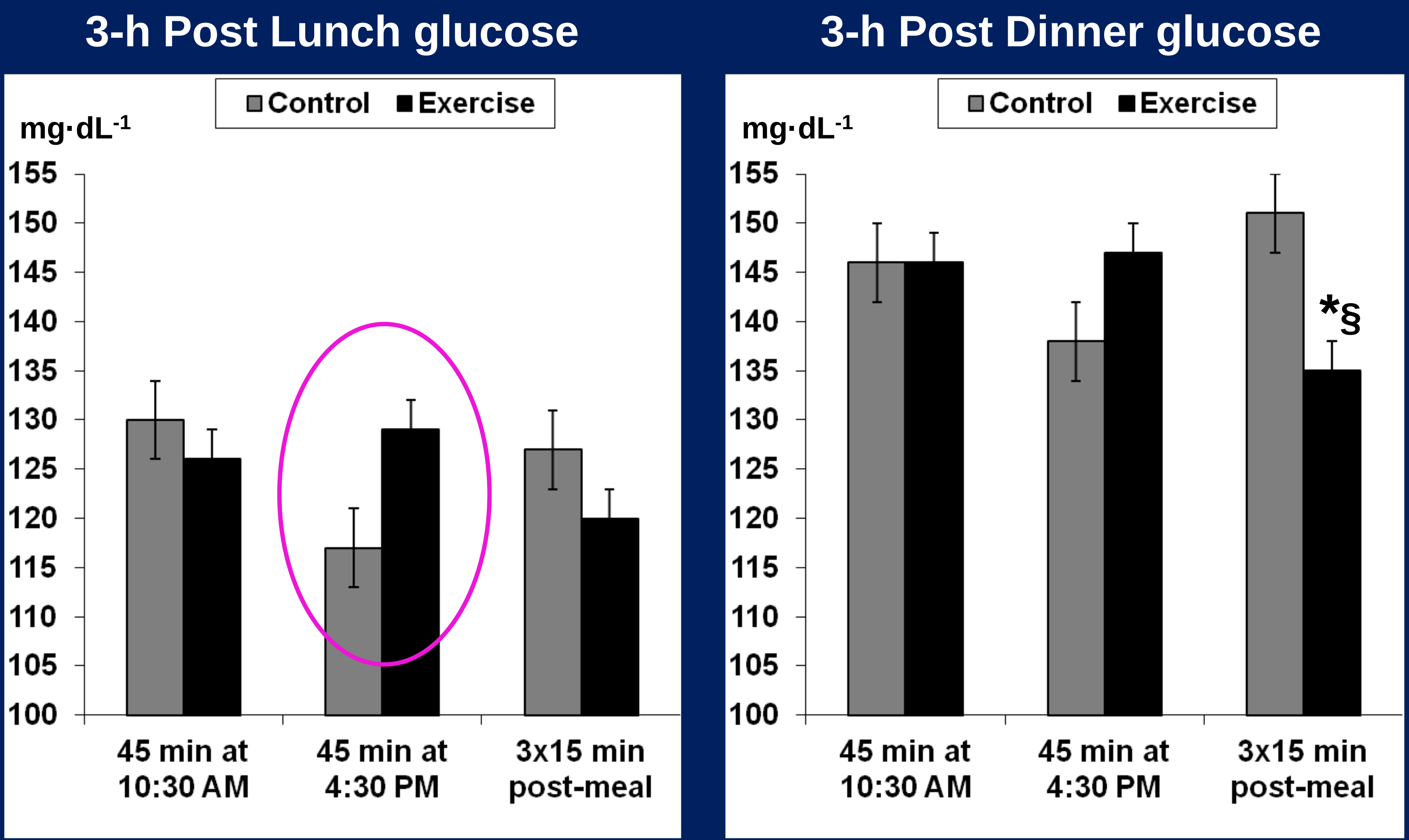
24-h averaged glucose (mg·dL^{-1})



*p<0.05 between control and exercise day. All walking performed on treadmill at a 3.0 MET exertion level.

DiPietro, et al. *Diabetes Care*. 36:2013

Figure 3. - Differences in 3-h post lunch (left) and 3-h post dinner (right) glucose concentrations between day 1 and day 2 by exercise prescription (N=10)

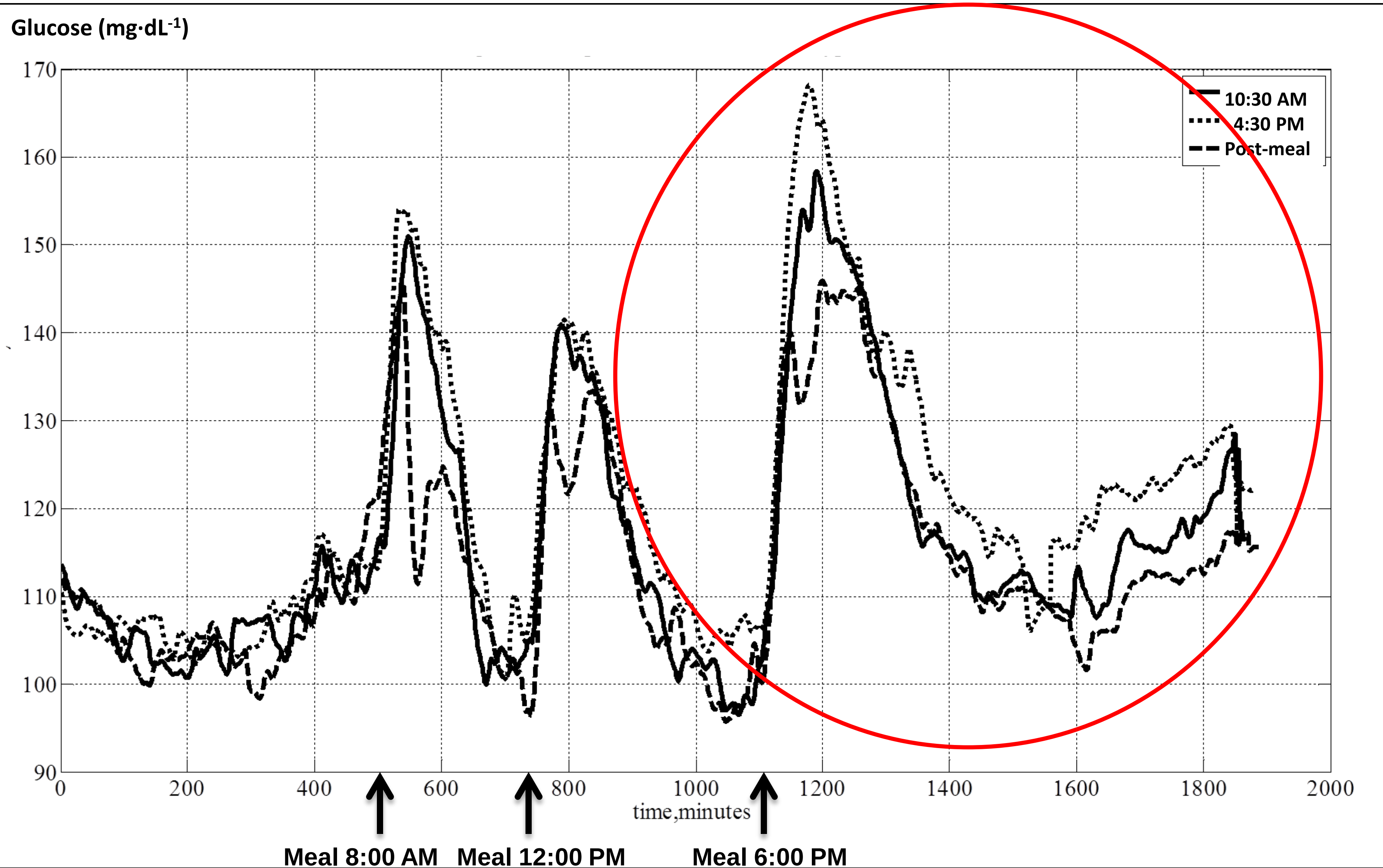


*p<0.01 between control and exercise day; § p<0.05 compared with sustained exercise in the morning or afternoon.

DiPietro L, et al, *Diabetes Care*, 2013

DiPietro L, et al, *Diabetes Care*, 2013

Figure 2.



Summary

- The benefits of high-intensity/high volume exercise are more enduring;
- Lower-intensity activity is less stressful, but has a more rapid decay and must be repeated daily to maintain benefits;
- Short bouts of lower-intensity activity that are timed after each meal are extremely effective for maintaining glycemic control – especially late in the day

Prolonged Sitting, Post-meal Walking, and Metabolic Responsiveness in Older People

NIH/NIA R56 AG050661

Metabolic Flexibility

- Defined as the ability of the cellular bioenergetics machinery to switch rapidly from one fuel source to another, in response to fuel availability, insulin, or exercise;

- A greater reliance on fatty acids for fuel, along with ability to conserve/replenish muscle glycogen was a survival advantage for hunting/gathering;

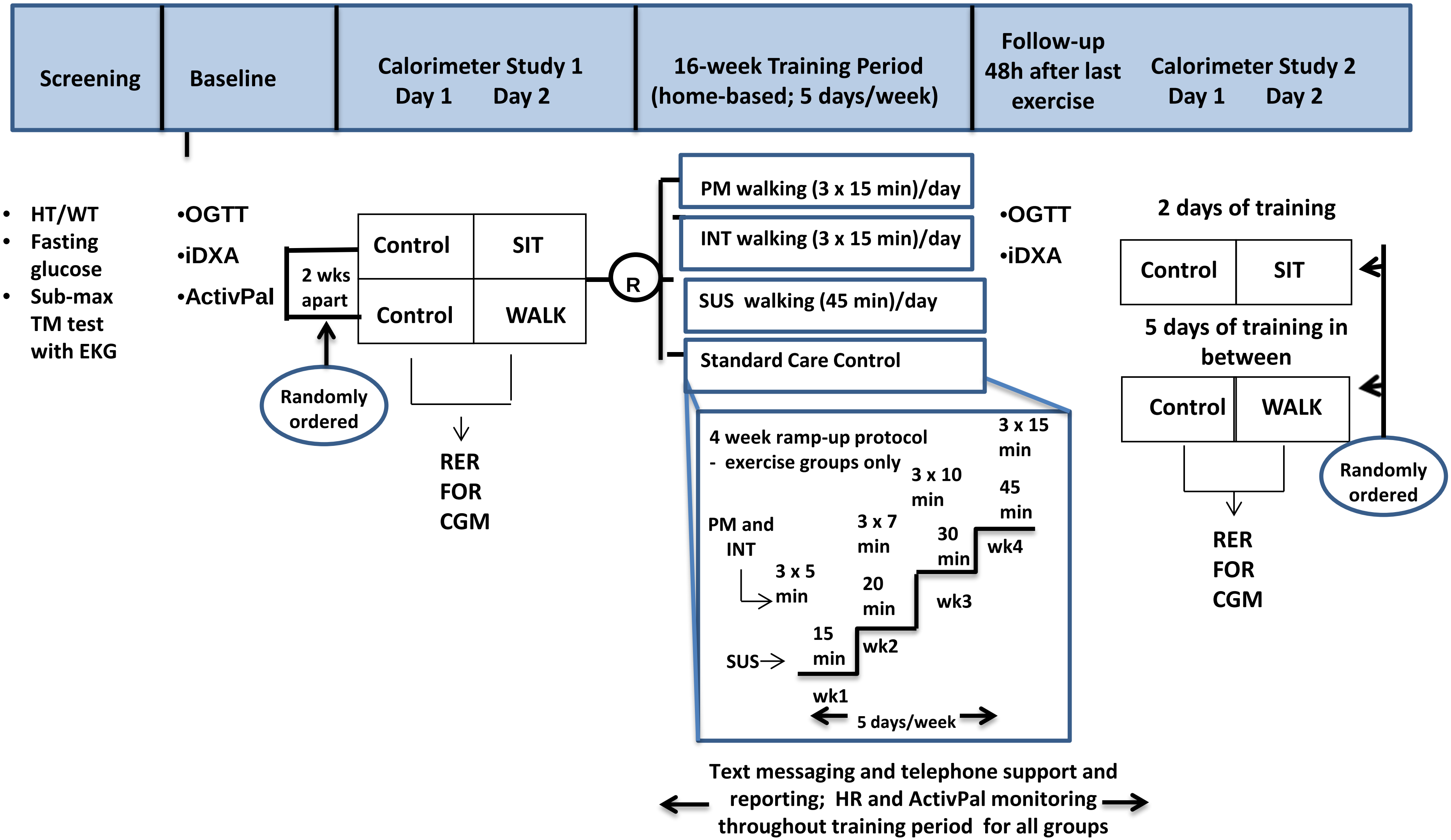
- Whole-body MF can be estimated quite accurately from the respiratory exchange ratio (RER=VCO_2/VO_2) using indirect calorimetry.

0.70 ◂– – – – – – – **RER** – – – – – – – –▸ **1.00**

Fats **Carbohydrates**

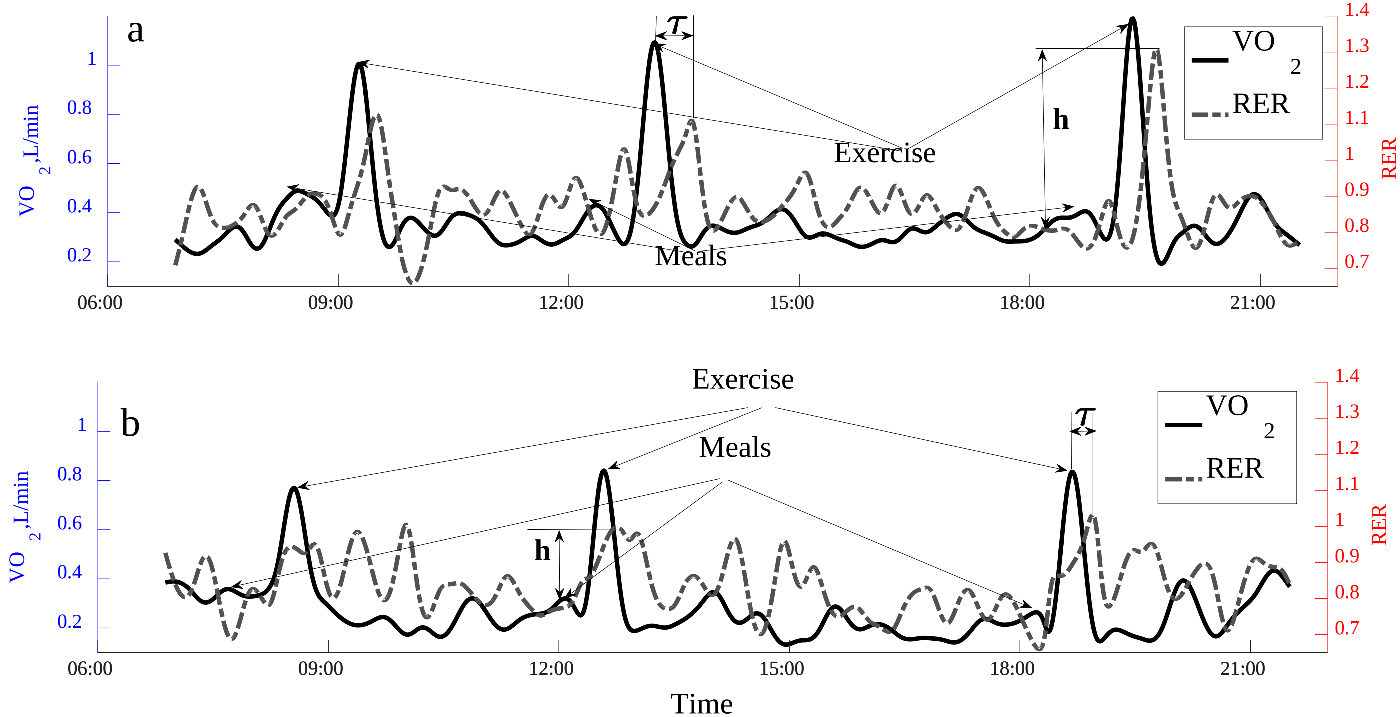
EXERCISE → ↑ Bioenergetic capacity of mitochondria ↑ Lipid metabolism ↑ Insulin sensitivity

Overall Study Protocol (N=80)



PA=physical activity assessment; SIT protocol =12h of sitting or reclining; WALK = [3 x 15 min post-meal TM walking at 3METs]; OGTT=3h oral glucose tolerance test with indirect calorimetry; iDXA=dual-energy x-ray absorptiometry for measurement of total fat (kg), visceral fat (kg), and lean mass (kg); RER=respiratory exchange ratio measured in calorimeter; CGM=continuous glucose monitoring; R=randomization to one of three training groups (n=15/group); FOR=fat oxidation rate; PM= intermittent post-meal exercise; INT=intermittent pre-meal exercise.

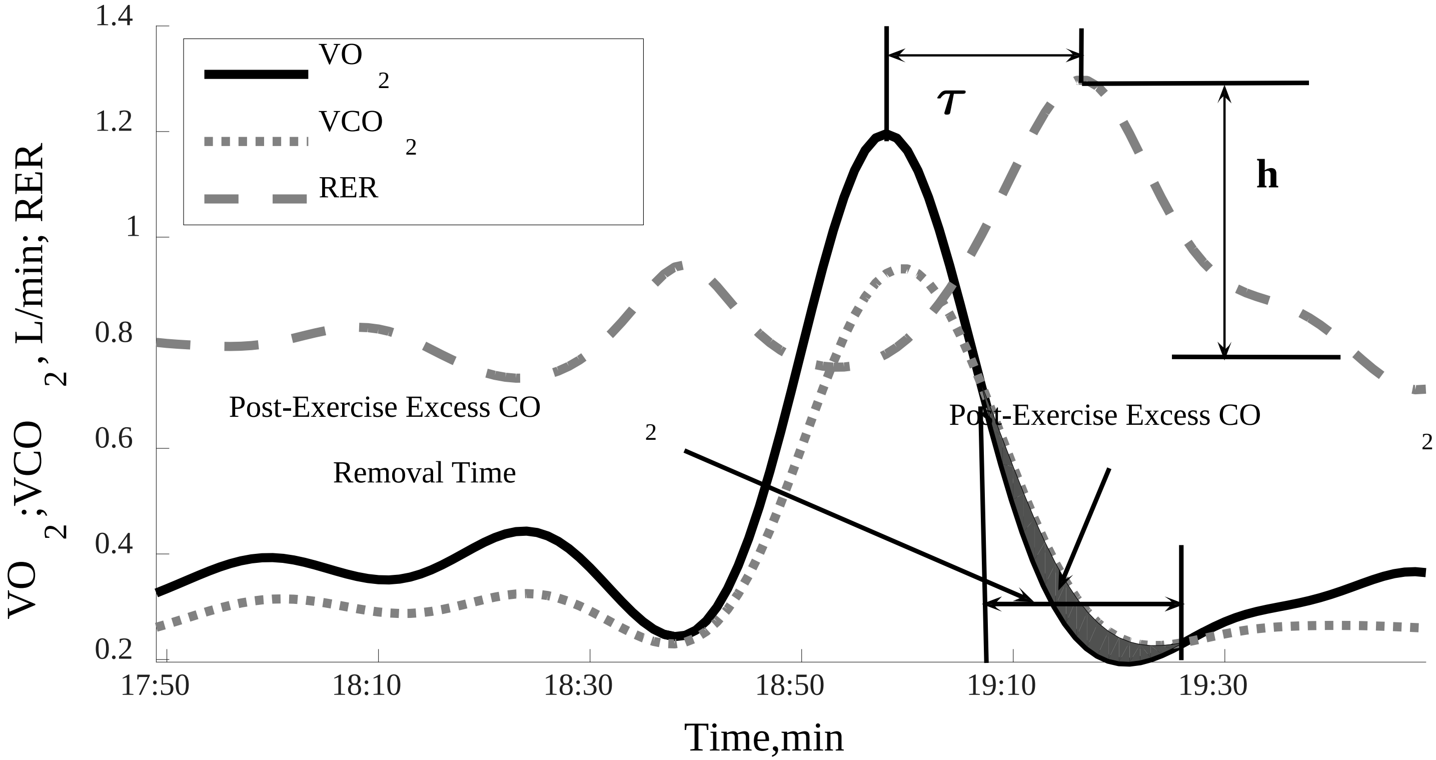
The relative kinetics of O_2 consumption and the respiratory exchange ratio (RER) in: a) an older woman with impaired glucose tolerance; and b) in an older woman normal glucose tolerance in response to three 15 min bouts of post-prandial treadmill walking (3 METs).



The dynamics of exercise-induced substrate oxidation were characterized by the height of the RER peaks in the post-exercise periods (h; calculated as the difference between resting baseline RER and the average post-exercise peak RER values) and the time lag between the peak of O2 consumption and RER peak (τ).

Gribok A, Rumpler W, and DiPietro L. *Diabetes Case Reports*. 2016.

The relative kinetics for the third post-prandial exercise period in a woman with IGT. The height (h) of the RER peak and their relative lag (T) demonstrate the dynamics of exercise-induced gas exchange and substrate oxidation.



Gribok A, Rumpler W, and DiPietro L. *Diabetes Case Reports*. 2016.

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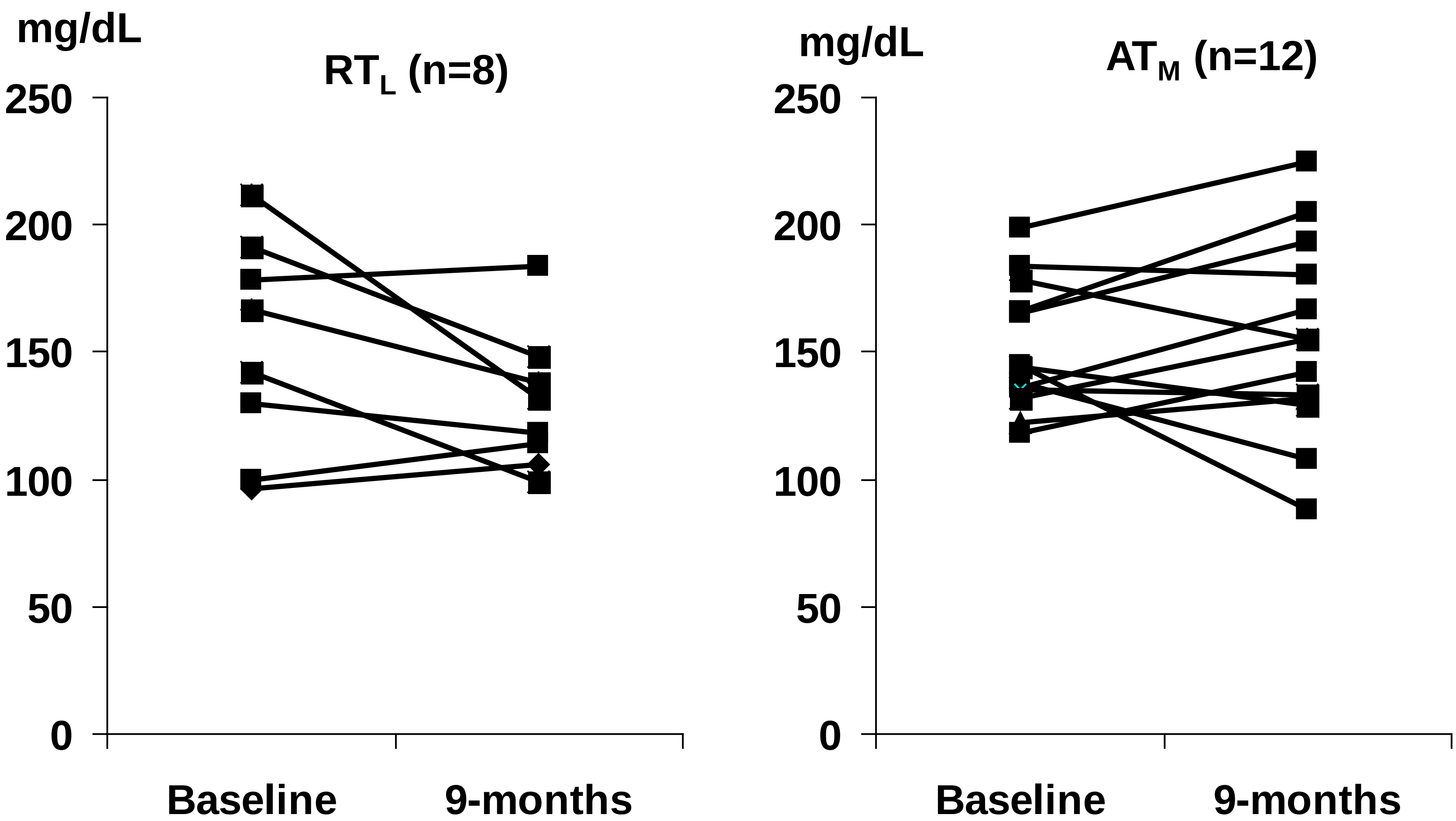
Individual changes in 2-h glucose concentrations before and after training



DiPietro, et al., *JPAH* 2008

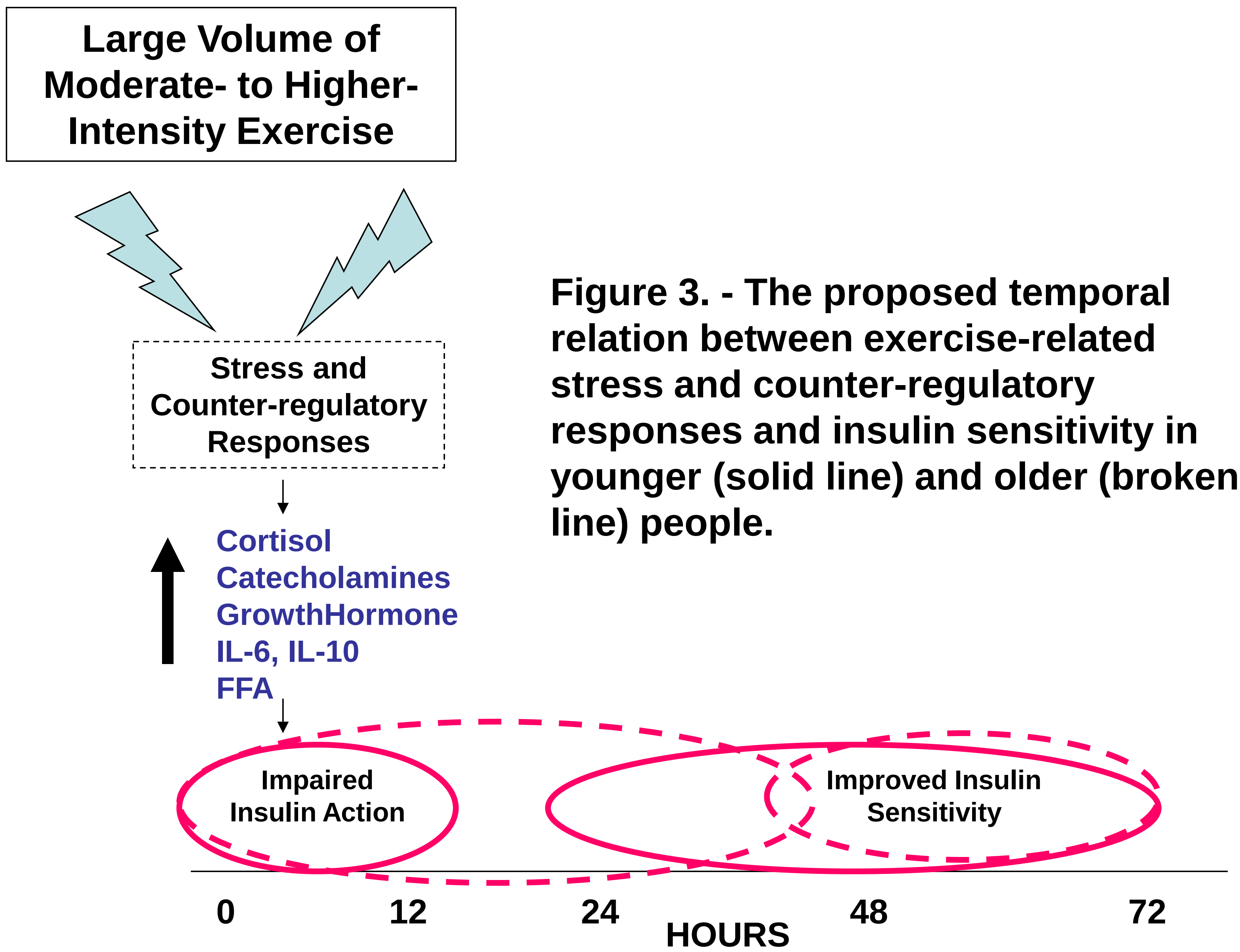
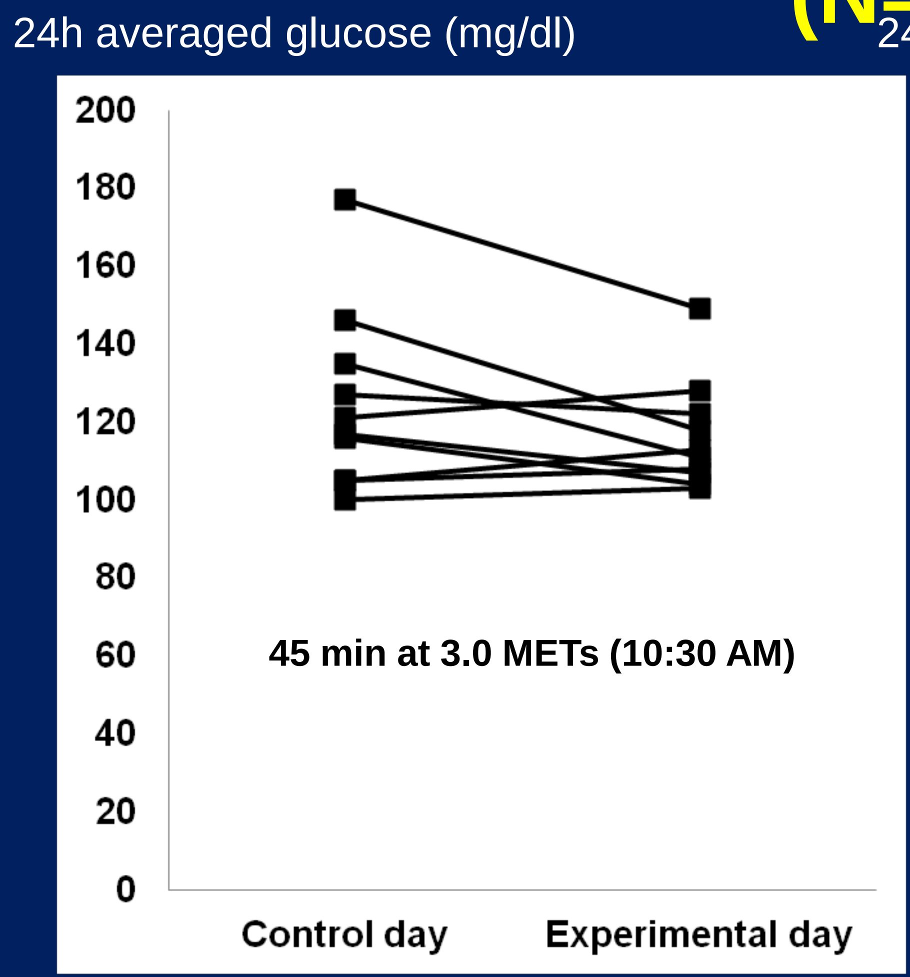
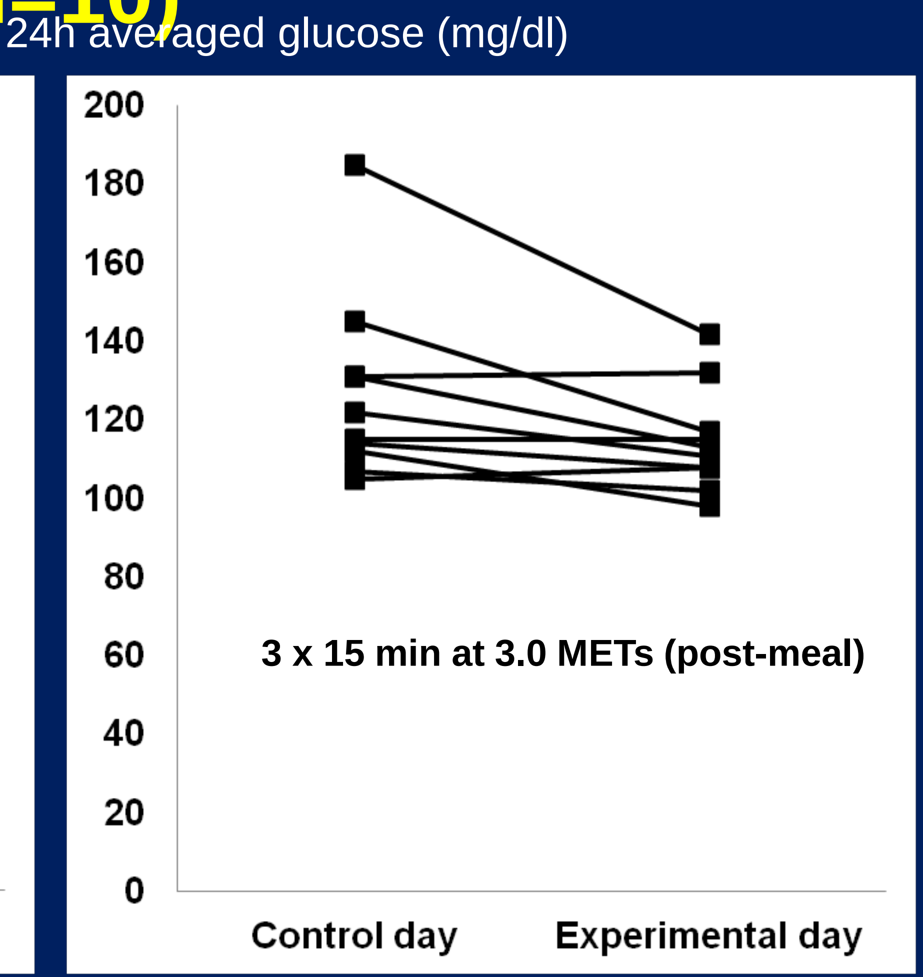


Figure 3. - The proposed temporal relation between exercise-related stress and counter-regulatory responses and insulin sensitivity in younger (solid line) and older (broken line) people.

Individual changes in 24h averaged glucose concentrations following sustained morning or post-meal walking (N=10)





DiPietro L, et al, *Diabetes Care*, 2013