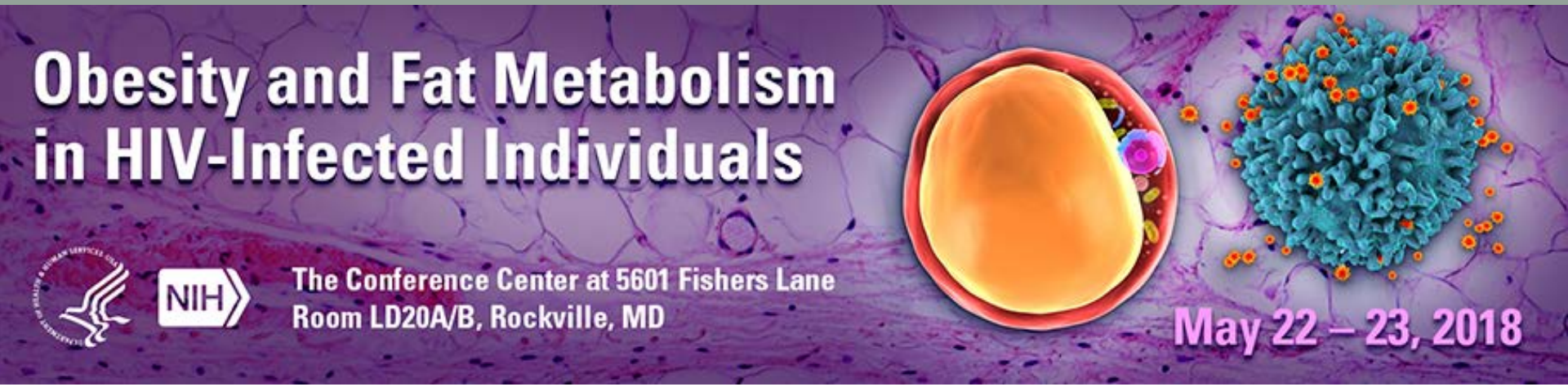

MEASURING Endpoints and Outcomes

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May 23, 2018 10:30-10:50 AM

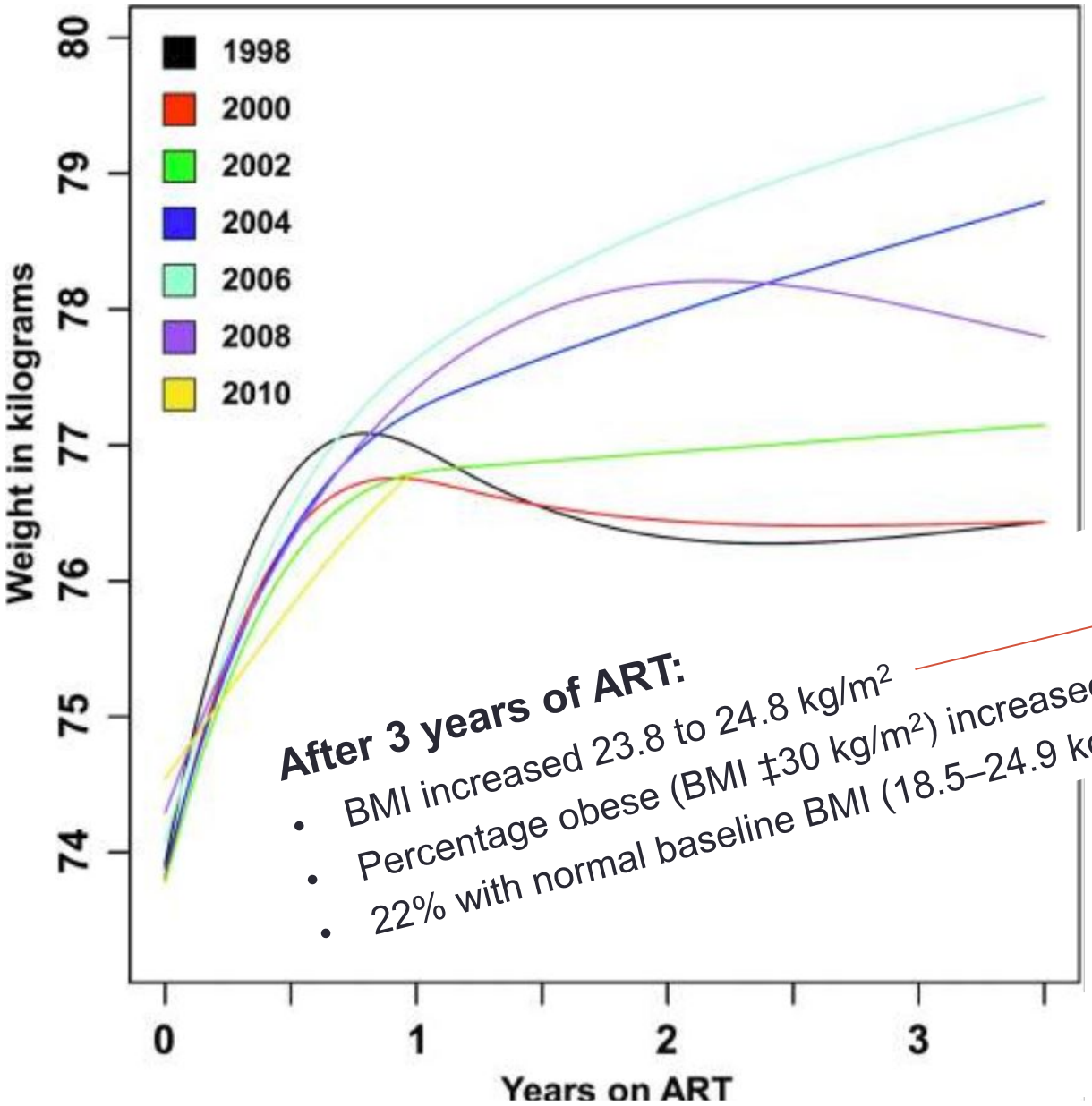
Benefits and Drawbacks of cART

Combination antiretroviral therapy (cART)

- Increases survival in HIV infected (HIV+) people
- Increases prevalence of obesity, metabolic syndrome, type 2 diabetes (T2D), and cardiovascular disease (CVD), particularly in women
- Adverse metabolic effects of obesity are especially pertinent in HIV, because HIV+ people already have a 2–4 fold increased risk of developing T2D and CVD than BMI-matched, HIV seronegative (HIV−) people
  - Although obesity increases the risk of T2D in people with HIV, increased BMI does not increase the risk of CVD events

Reeds DN, et al. Obesity (Silver Spring). 2017 Apr;25(4):682-688.

Estimated Mean Weight Over Initial 3 Years Following ART Initiation



After 3 years of ART:

- BMI increased 23.8 to 24.8 kg/m^2
- Percentage obese (BMI ‡30 kg/m^2) increased 9% to 18%
- 22% with normal baseline BMI (18.5–24.9 kg/m^2) became overweight

- 14,084 pts from 17 cohorts
- 83% male, 57% nonwhite
- Median age 40 years

Koethe JR, et al. AIDS Res Hum Retroviruses. 2016 Jan;32(1):50-8.

Does HIV infection prevent the metabolic benefits of lifestyle change and/or moderate, diet-induced weight loss in men and women?

What evidence is there in the literature to date?

What outcomes were measured?

Measures of Metabolic Risk

- Body Mass Index, WC and Body Composition (DEXA scan) visceral and subcutaneous compartments MRI

- NCEP ATP III criteria for **Metabolic Syndrome**: any three of the five criteria:
- WC > 40 (men) > 35 inches (women)
- Fasting glucose > 100 mg/dl
- TG > 150 mg/dl
- HDL cholesterol < 40 (men) < 50 mg/dl (women)
- BP > 130 mmHg systolic or > 85 mmHg diastolic

- **Insulin Sensitivity:**
- HOMA-IR
- Oral Glucose Tolerance Test 75 gm
- FS IVGTT
- 2 stage hyperinsulinemic euglycemic clamp

- Inflammation: serum hs CRP, IL-6, TNF
- Inflammation: adipose tissue mRNA gene expression

Does HIV infection prevent the metabolic benefits of moderate, diet-induced weight loss in women?

Yes

- 18 HIV-infected women with BMI > 30 kg/m^2 completed a 12-week weight loss program
- Low-calorie diet in combination with a supervised exercise program

RESULTS at follow-up

- 7% weight loss – and fat mass loss (DEXA)
- Improvements in strength, fitness, and QOL
- No improvement in fasting glucose, insulin, or insulin sensitivity by fsIVGTT
- No change in fasting lipids, tissue plasminogen activator (PAI), or PAI-1
- No significant change in CD4 count or HIV viral load

Engelson ES, et al. Metabolism. 2006 Oct;55(10):1327-36.

Does HIV infection prevent the metabolic benefits of moderate supervised exercise in men and women

Yes

Supervised 4 day per week exercise program in 92 men/women for 3 months with no control group:

- Lifestyle therapy (exercise alone) in patients with HIV infection resulted in a decrease in waist circumference without a change in body weight
- Increase in muscle strength and decrease in diastolic blood pressure
- Failed to show any other beneficial metabolic benefits – no change in lipids, hs CRP, systolic BP

Fitch KV, et al. AIDS. 2006 Sep 11;20(14):1843-50.
Cutrono SE, et al. AIDS Behav. 2016 May;20(5):1123-31.

Does HIV infection prevent the metabolic benefits of moderate, diet-induced weight loss in men/women

DPP style lifestyle program versus control arm for 6 months in 34 subjects with HIV and metabolic syndrome:

- Lifestyle therapy in patients with HIV infection resulted in a decrease in waist circumference without a change in body weight
- Systolic blood pressure and HbA1c decreased; no change in HOMA
- Lipid levels DID NOT improve, however

Yes

Fitch KV, et al. AIDS. 2006 Sep 11;20(14):1843-50.
Cutrono SE, et al. AIDS Behav. 2016 May;20(5):1123-31.

Does HIV infection prevent the metabolic benefits of moderate, diet-induced weight loss in women?

No

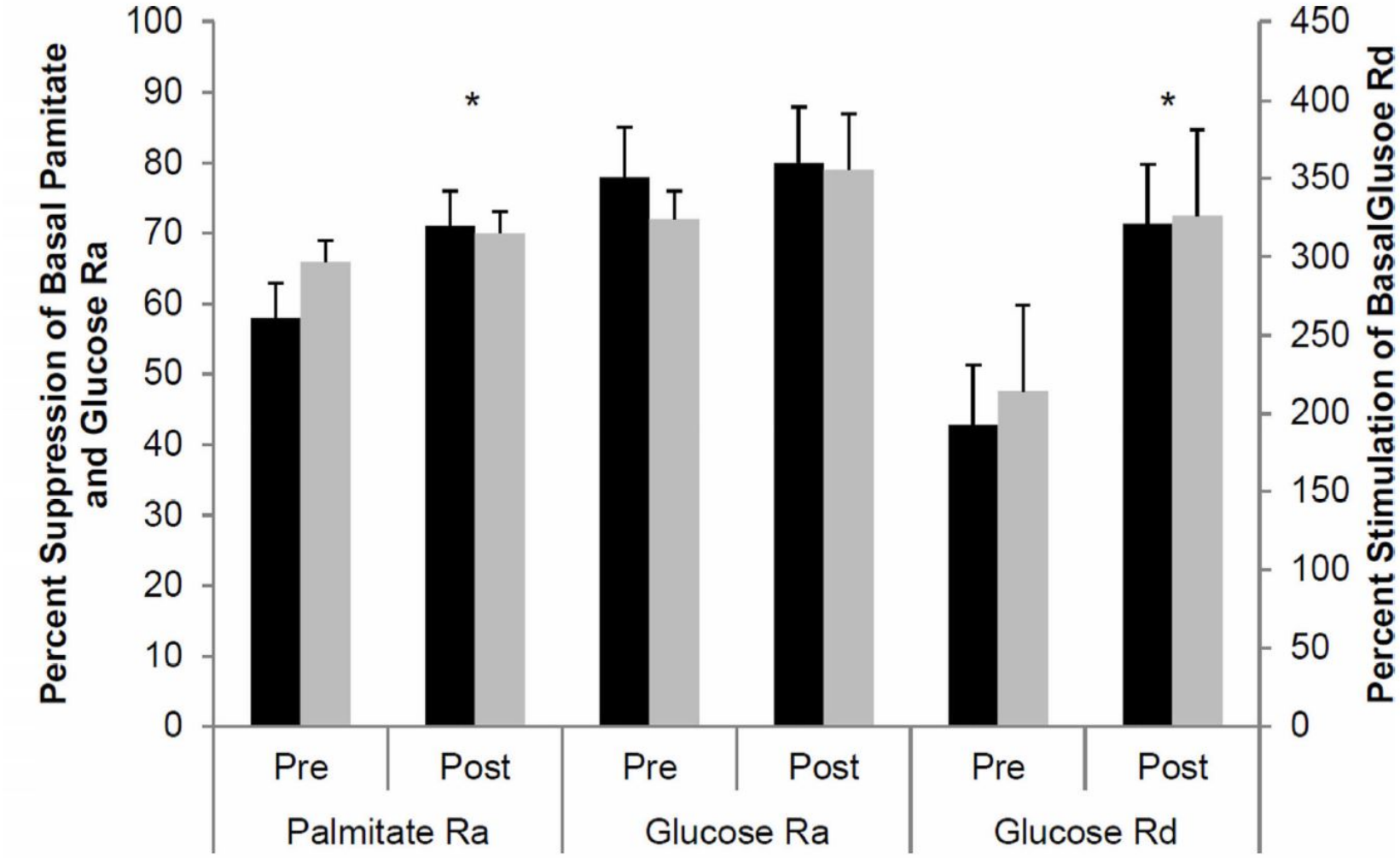
- 20 women who were obese and HIV+ (age 37±2 yrs, BMI 43.8±2.9 kg/m^2 17 AA, 3 Caucasian)
- 8 women who were obese and HIV− (age 40±1 yrs, BMI 39±2 kg/m^2, 6 AA, 2 Caucasian)
- 1000 kcal/day deficit and dietary counseling
- 2 stage hyperinsulinemic euglycemic clamp with tracer glucose and palmitate infusions
- Adipose tissue biopsies

RESULTS at follow-up

- ~7.5% weight loss in both groups
- Decrease in fat-free-mass >in HIV+ than HIV− subjects (−4.4±0.7 % vs −1.7±1.0%, P < 0.05)
- Improved insulin-sensitivity in adipose-tissue (suppression of palmitate rate of appearance [Ra]), liver (suppression of glucose Ra) and muscle (glucose disposal) similar in both groups
- Weight-loss did not affect adipose-tissue expression of markers of inflammation or ER stress in either group

Reeds DN, et al. Obesity (Silver Spring). 2017 Apr;25(4):682-688.

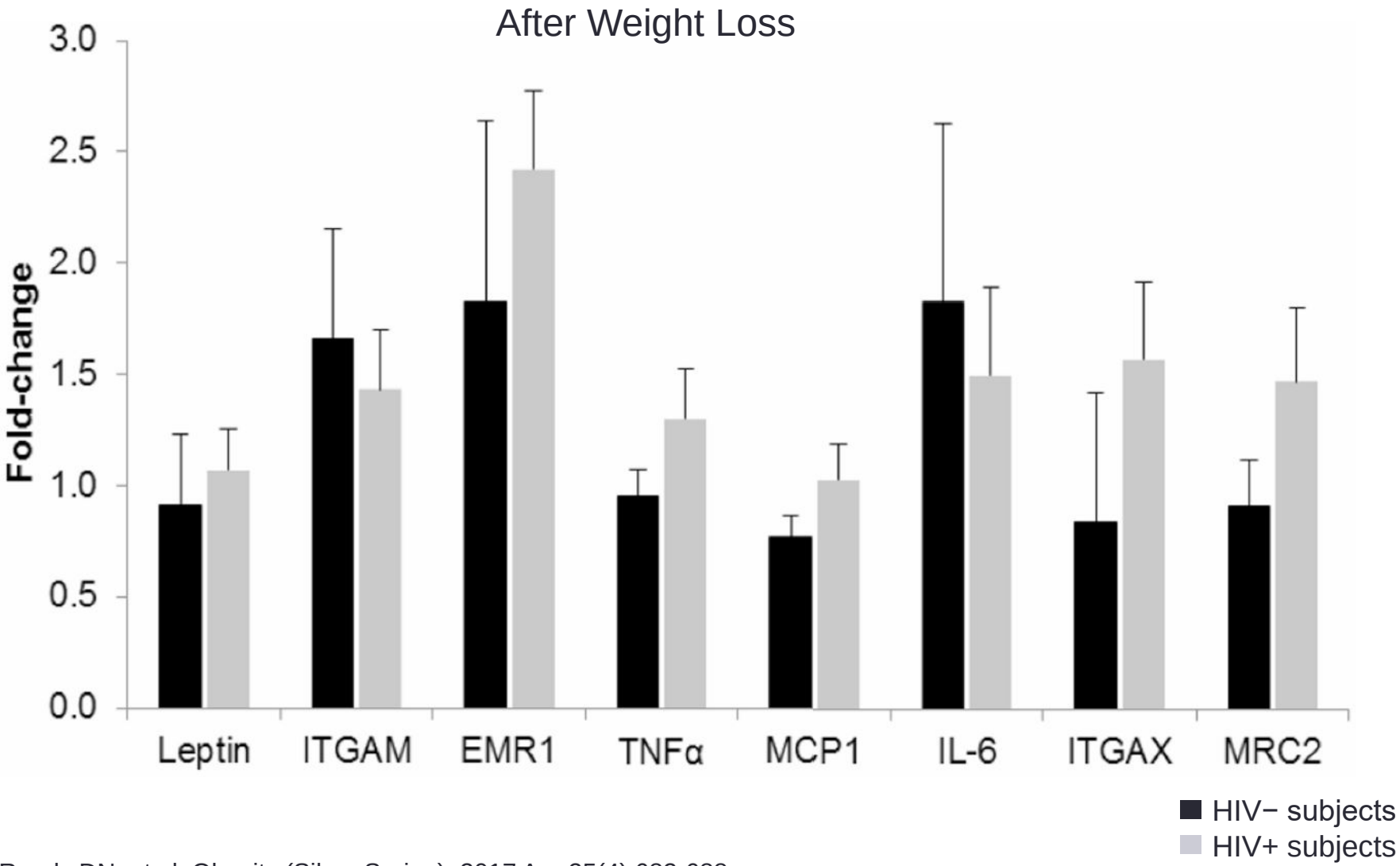
Percent Suppression of Palmitate and Glucose Ra and Stimulation of Glu Rd



* Main effect of time, P < 0.05

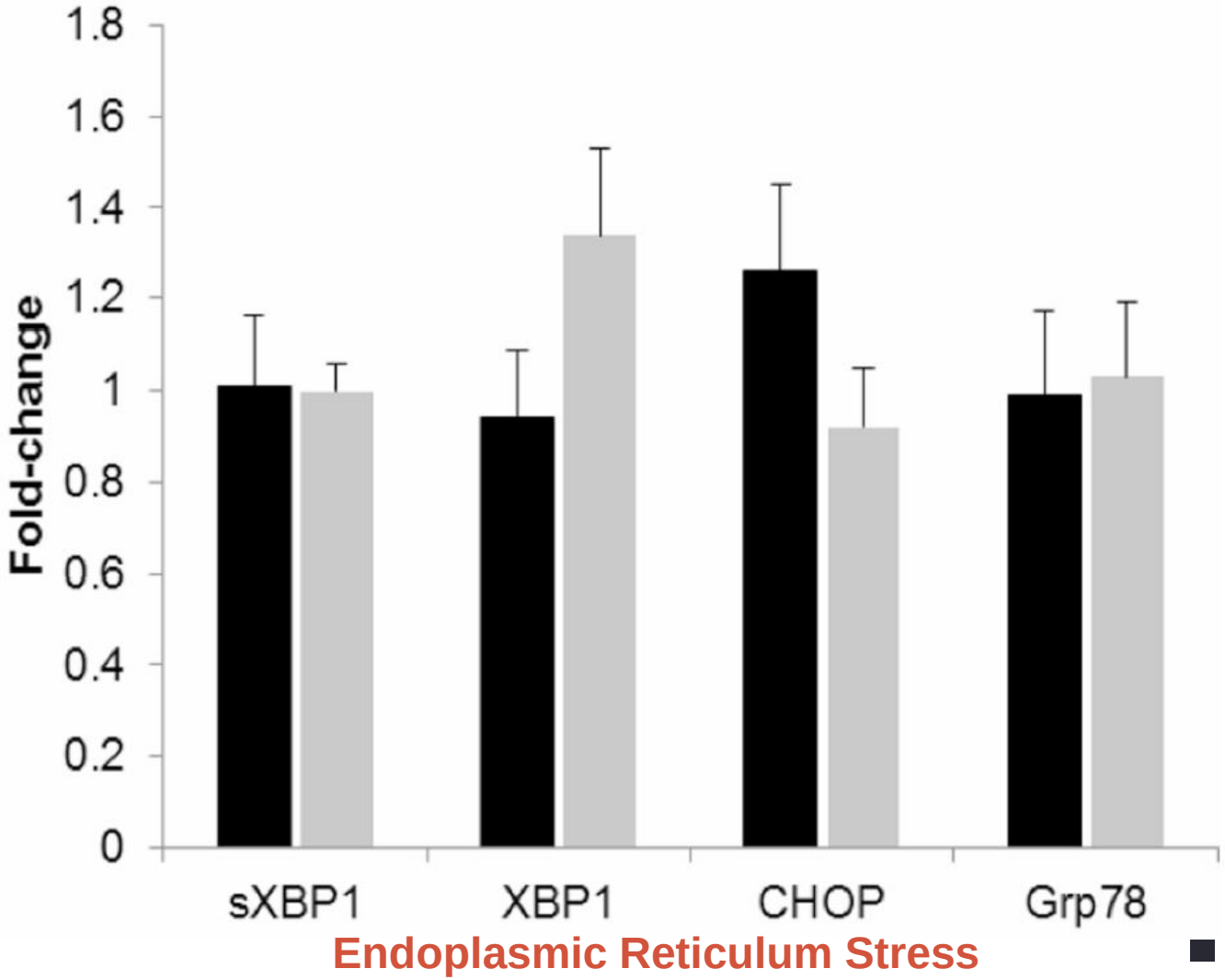
Reeds DN, et al. Obesity (Silver Spring). 2017 Apr;25(4):682-688.

Fold-changes in Adipose Tissue Gene Expression of Markers of Inflammation



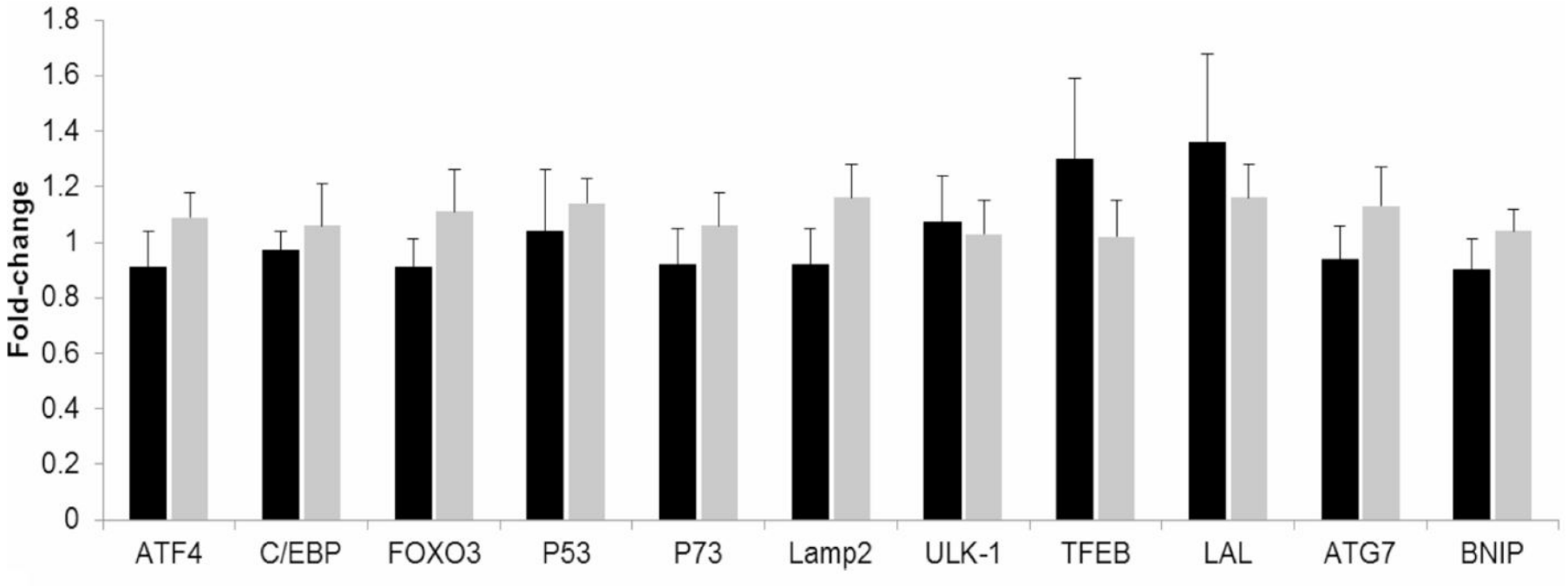
Reeds DN, et al. Obesity (Silver Spring). 2017 Apr;25(4):682-688.

Fold-changes in Adipose Tissue Gene Expression of Markers of ER Stress



Reeds DN, et al. Obesity (Silver Spring). 2017 Apr;25(4):682-688.

Fold-changes in Adipose Tissue Gene Expression of Markers of Autophagy



After Weight Loss

HIV− subjects
HIV+ subjects

Reeds DN, et al. Obesity (Silver Spring). 2017 Apr;25(4):682-688.

Body Composition and Cardiometabolic Variables Before and After Weight Loss

	HIV−			HIV+		
	Before	After	% Difference	Before	After	% Difference
Body weight (kg)	113	105	−7.3*	108	100	−7.7*
BMI (kg/m2)	39.9	36.9	−7.1*	39.1	36.3	−7.2*
Fat-free mass (kg)	55.7	54.8	−1.7	51.1	48.9	−4.4
Appendicular FFM (kg)	25.5	25.4*	−0.6	25.2	23.7*,	−5.8
Fat mass (% body wgt)	45.9	44.0	−4.4*	49.7	48.0	−3.2*
Total abdominal AT (cm3)	5052	4815	−6.4*	5227	4757*	−7.4*
Visceral AT (cm3)	1139	1034	−12*	1164	997*	−14*
VAT:TAT ratio	0.22	0.22	−5.1*	0.24	0.22*	−7.1*
IHTG content (%)	7.5	5.4	−16.8*	4.6	2.2*	−26.3*
Systolic BP (mmHg)	126	117	−7*	122	118	−4*
Diastolic BP (mmHg)	76	69	−9*	72	69	−4*
Glucose (mg/dl)	91.5	87.6	−4.0	94.1	91.7	−2.2
Insulin (μU/L)	18.3	8.8	−54.0	16.6	14.2	−11.1
C-peptide (ng/ml)	3.2	2.2	−28.2	2.8	2.7	−3.9
Leptin (μg/L)	39.0	36.2	−8.6*	53.1	39.8	−20.4*
Hemoglobin A1C (%)	5.8	5.3	−7.9	5.7	5.6	−3.2
FFA (μmol/ml)	550	527	−3.1	661q	662	−1.1
LDL-C (mg/dl)	111	100	−9	103	101	−1
HDL-C (mg/dl)	43	39	−9*	42	39	−7*
Triglyceride (mg/dl)	128	92	−17	112	119	12

Reeds DN, et al. Obesity (Silver Spring). 2017 Apr;25(4):682-688.

*P<0.05 for main effect of time

Body Composition Assessments

- Body fat and fat-free mass (FFM) were determined by using dual-energy-X-ray absorptiometry
- Visceral and abdominal subcutaneous adipose tissue volumes were quantified by using magnetic resonance imaging
- Intrahepatic triglyceride content was measured by using magnetic resonance spectroscopy

MRI was not able to be performed in 4 HIV+ subjects and 2 HIV− subjects

Reeds DN, et al. Obesity (Silver Spring). 2017 Apr;25(4):682-688.

Reasons for different findings among similiar studies: studies were really not similar

Differences in Treatments (Diet and Exercise)

Differences in cART Regimens

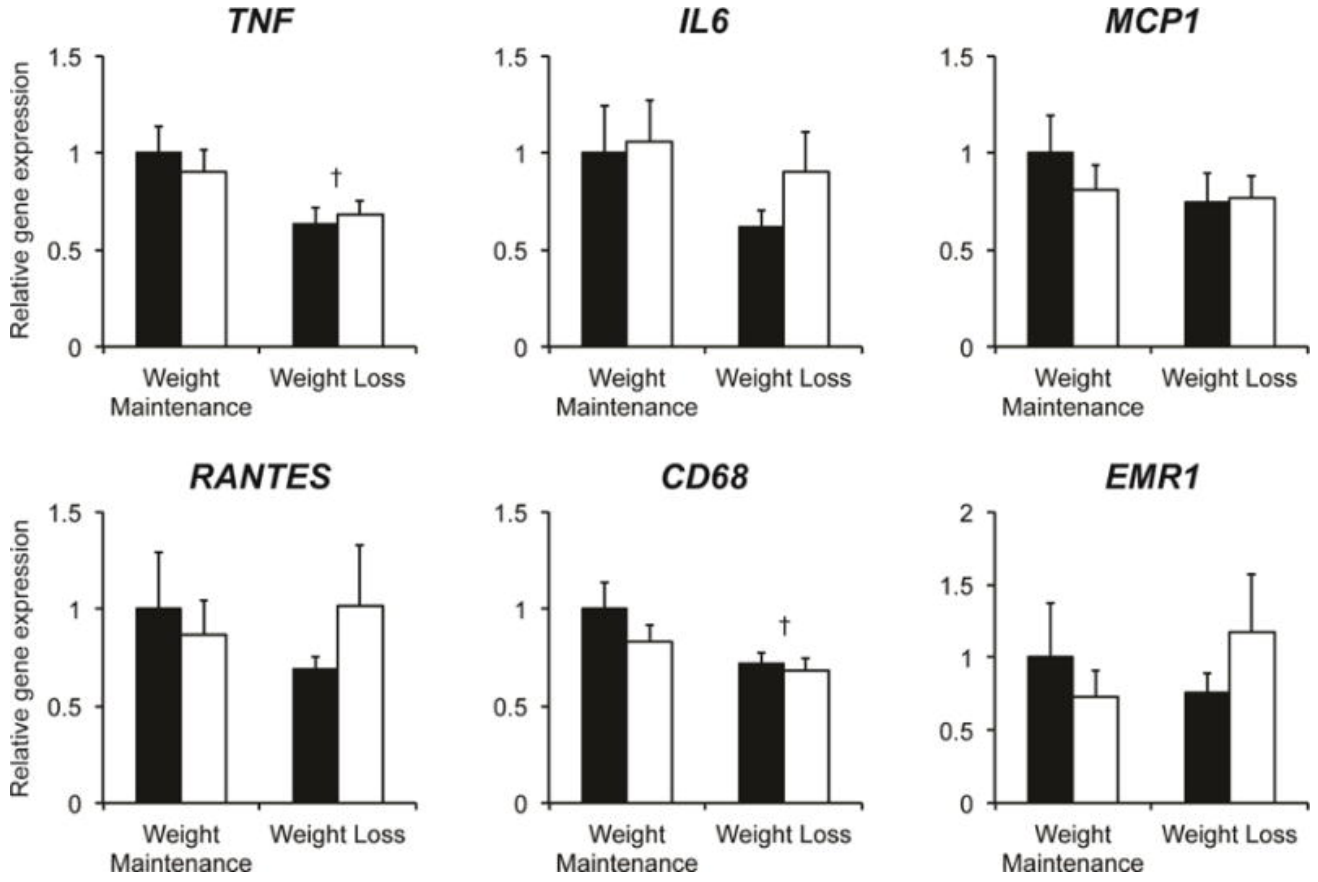
- Ritonavir boosted darunavir or atazanavir and emtricitabine with tenofovir, could have less adverse metabolic effects than older (unspecified) PIs

Differences in Testing for Insulin Sensitivity

- Two-stage hyperinsulinemic-euglycemic clamp procedure in conjunction with a stable isotopically labeled glucose tracer infusion is a more sensitive measure of insulin action than frequently-sampled intravenous glucose tolerance tests; also measured adipose tissue insulin sensitivity with labelled palmitate

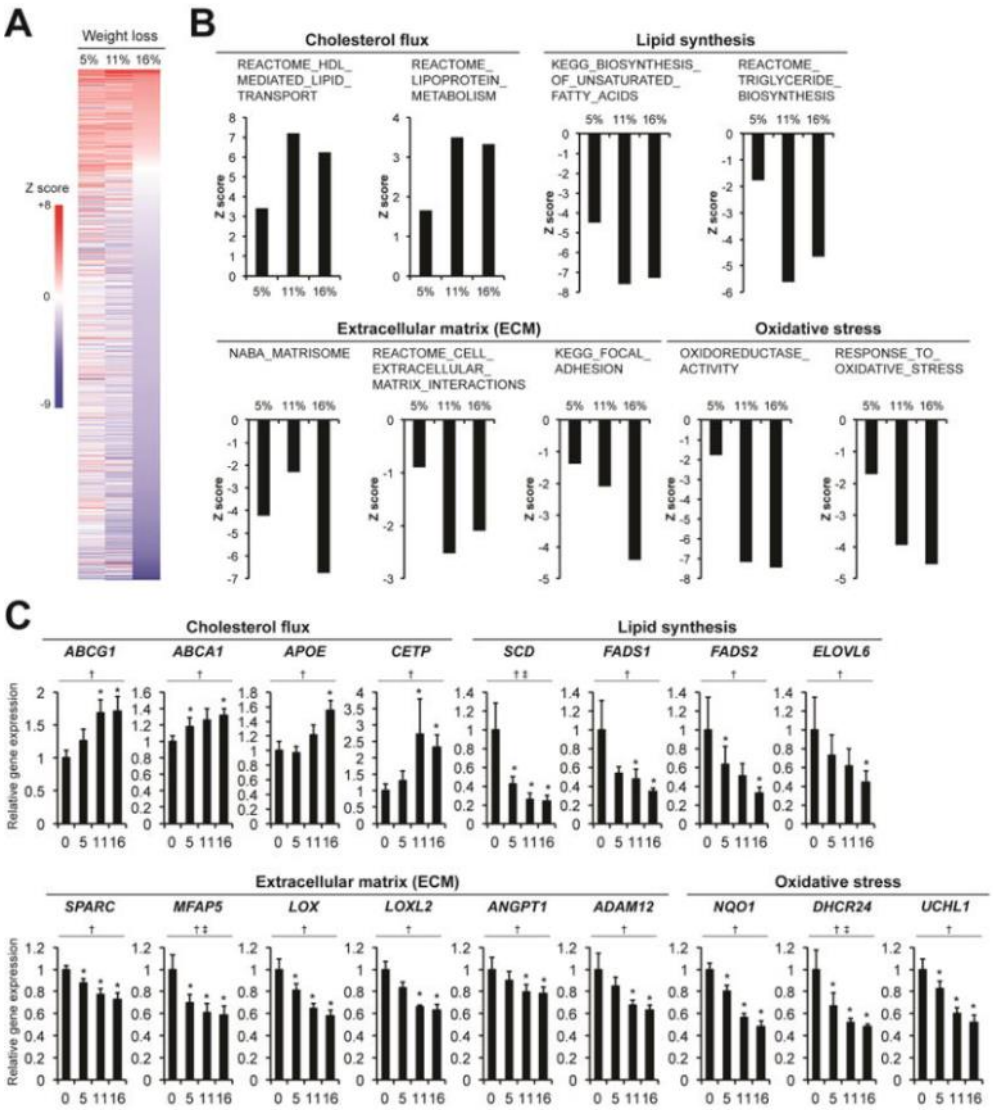
Reeds DN, et al. Obesity (Silver Spring). 2017 Apr;25(4):682-688.

Effect of 5% weight loss on subcutaneous adipose tissue gene expression of inflammatory markers



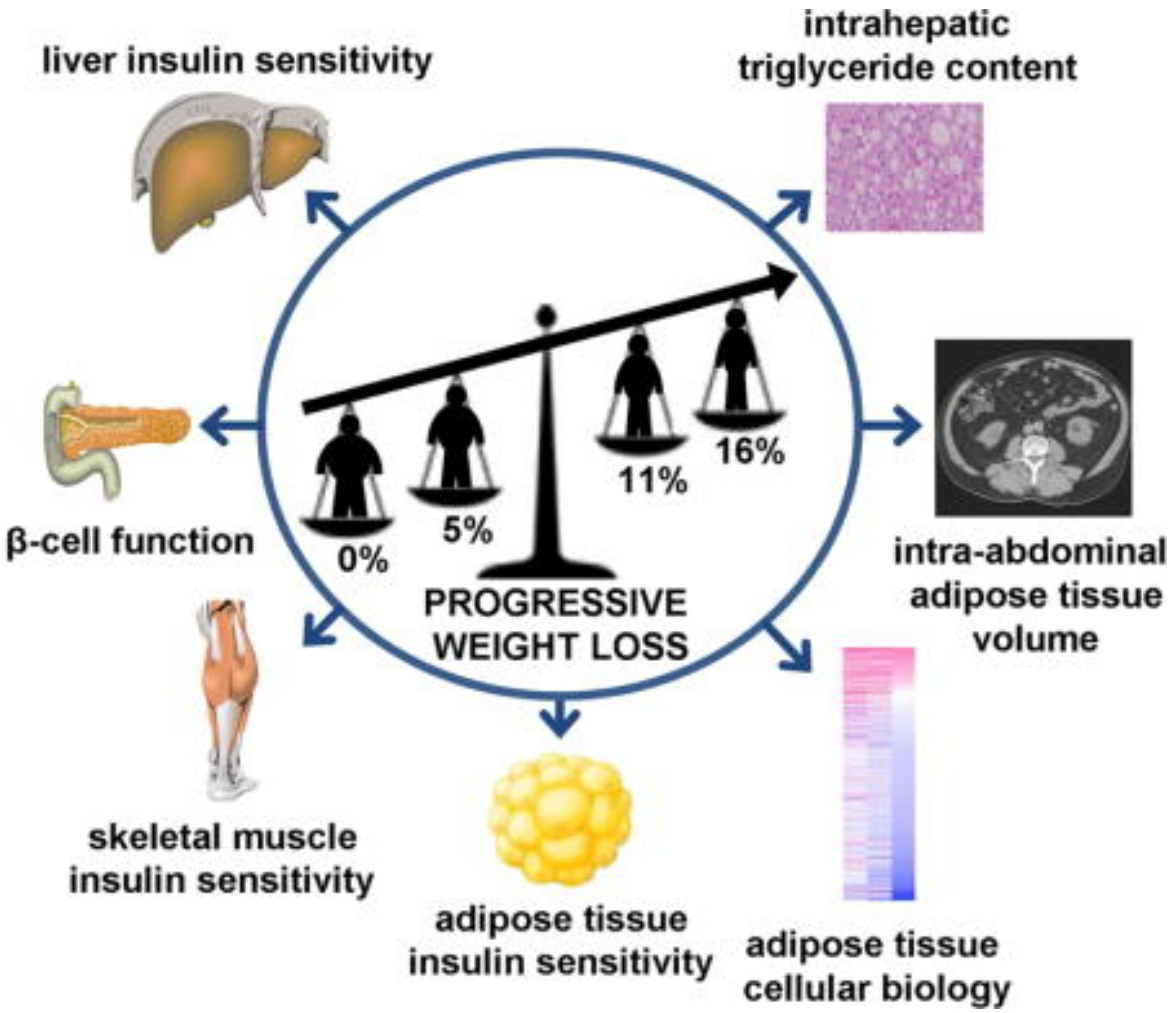
Magkos F, Klein S. Cell Metab 2016; 23:591-601.

Effect of progressive weight loss on subcutaneous adipose tissue gene expression profile



Magkos F, Klein S. Cell Metab 2016; 23:591-601.

Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity



Magkos F, Klein S. Cell Metab 2016; 23:591-601.

Conclusions – Endpoints and Outcomes

- It is important to add **body composition outcomes** to markers of improvement in HIV positive patients after weight loss
  - Such as body composition by DEXA
- Also measures of inflammation such as **hs CRP** and **IL 6** in the blood
- Testing for glycemic parameters:Bergman minimal model fsIVGTT if you cannot perform clamps
- For research purposes to test benefits of various weight loss strategies – **adipose tissue biopsies** to look at histology and gene expression
- This would assist in assessing the benefits of weight loss in combination with androgens such as testosterone for FFM, resistance exercise training and leptin treatment

Weight Loss in HIV : Outcomes to consider based on literature

- FFM loss larger in HIV positive persons – insulin resistant protein metabolism?
- Consider measures of body composition and muscle strength and function

- Drop in insulin levels much less pronounced in HIV + and there is a persistent basal hyperinsulinemia
- Consider gold standard 2 stage hyperinsulinemic euglycemic clamp

- Outcomes and endpoint measures differ based on amount of weight loss achieved: 5-10% versus 11-16% weight loss
- Consider adipose tissue analysis for greater weight losses

Outcomes- Muscle Mass and Function

Primary

Change in whole body lean mass, measured by DXA

Secondary

- **Appendicular and trunk lean and fat mass**
- **Tests of Muscle Performance**
  - Maximal voluntary strength in leg press and chest press exercise
  - Leg power
- **Tests of Physical Function and Task-Specific Performance**
  - 6-minute walking distance and speed
  - Stair-climbing power and speed – unloaded and loaded
  - 50-meter timed walk with 20% load carry
- **Physical function domain of the MOS SF-36**
- **Wellbeing measures:**
  - Psychological Well Being Index
  - Derogatis Affective Balance Scale (DABS)
- **Fatigue by FACIT-1 Fatigue scale**
- **Hormone Levels**

Bhasin S, Apovian CM, Travison TG, et al. JAMA Intern Med. 2018 Mar 12. [Epub ahead of print].

Beyond the Body Mass Index (BMI)

- Worked well during the 1990s – the earlier days of bariatric surgery when predominantly BMIs over 50 underwent the procedures
- Critical tool for population studies
- In clinical setting – fails to reflect body composition
- Unigender value – however at BMI of 35, % fat in females is 46% compared to 35% in males
- Discriminates by fitness
- Discriminates by age
- Discriminates by race – similar distributions of glucose and lipid factors at lower BMI values in South Asians Chinese and Aboriginal people compared to Europeans

Pories WJ, Obesity 2010;18:865-871

The Future: 3-dimensional Body Composition Analysis

Styku

Scan Report

Basic Info — DIANA THOMAS

Profile		Fitness & Health Metrics	
Your profile information		Wellness Information	
Full Name	Diana Thomas	Body Fat %	24.1% (Average)
Age	47	BMI	20.9
Gender	Female	Body Volume	3163 in³
Height & Weight	5 ft 4 in & 122 lbs	Waist-to-Hip Ratio	0.754 (low risk)
Email	diana.thomas@usma.edu	Health Risks	
Scan Date	6/2/2017 3:12:13 AM	BMR	1259 Calories/day
Location	Usma	Percentile	70% for your gender and age

Better Predictor of Risk Due to Adiposity than BMI – the BAI

Body Adiposity Index (BAI) is defined as :

- 18

$$BAI = \frac{Hip}{Height\ \sqrt{Height}} - 18$$

BAI was found to be strong predictor of % body fat validated against DEXA in Mexican Americans and confirmed in African Americans

In contrast to the BAI, the relationships between %fat and the BMI itself for males and females lie on very different linear representations, as has been reported previously.

For example, the BMI value defined for obesity, BMI in the range between 27 and 28 kg/m^2 in this population, corresponds to a %adiposity of 23.6 ± 3.7 for men, vs. 34.3 ± 2.9 for women.

Bergman RN et al. Obesity 2011; 19(5):1083-9.

Outcomes to assess metabolic and ectopic fat after weight loss in HIV

- Baseline and post intervention assessment included fasting blood sampling for lipids, IGF-1, CBC, T-cell subsets, HIV viral load, hemoglobin A1c (HbA1c), c-reactive protein (CRP), adiponectin, AST, and alanine aminotransferase (ALT); 75g oral glucose tolerance test (OGTT); waist and hip circumferences; dual-energy x-ray absorptiometry (DXA, Hologic, Discovery A) for total body and regional fat mass; singleslice computed tomography (CT) at L4 for assessment of visceral and subcutaneous adipose tissue (SAT) area12,13; 1H magnetic resonance spectroscopy (MRS) for hepatocellular lipidto-water percent (HCL/W%) and intramyocellular lipid (IMCL) of the tibialis anterior and soleus muscles

Stanley T, Grinspoon S. JAMA. 2014 July 23; 312(4): 380–389. doi:10.1001/jama.2014.8334.