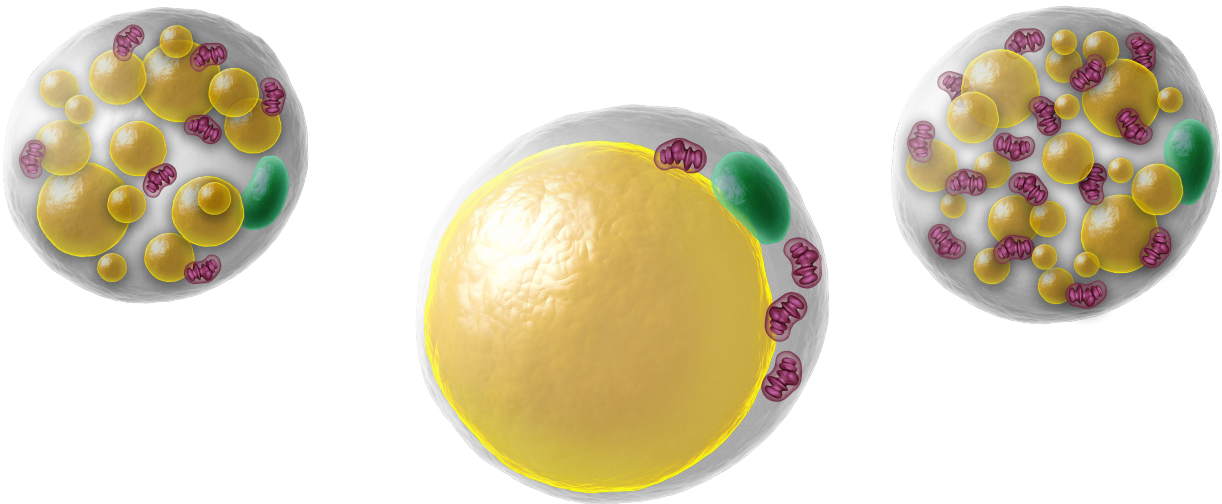


**Internal Medicine Grand Rounds
University of Texas Southwestern Medical Center**

January 25, 2019

**Adipose Tissue in Health and Disease:
Why Should We Care?**

Phil Scherer, PhD



This is to acknowledge that Phil Scherer, PhD has disclosed no financial interests or relationships with commercial concerns directly or indirectly related to this program. Dr. Scherer will not be discussing any off-label uses in his presentation.

Presenter: Phil Scherer, PhD

Rank: Professor

Division: Touchstone Diabetes Center

Purpose & Overview:

To discuss and explain the underlying mechanisms responsible for the development of diabetes and the underlying pathophysiological changes in adipose tissue. The adipocyte is a major endocrine cell whose contribution to systemic carbohydrate and lipid homeostasis are frequently underestimated.

Objectives:

1. Know about the role of adipocyte-derived factors in insulin sensitivity and lipid metabolism
2. Gain insights into the mechanisms of local adipose tissue dysfunction in obesity and its impact on lipid metabolism.
3. Interpret cellular aspects of contributions of adipocytes to systemic lipid homeostasis

Biosketch:

Philipp Scherer is Professor and Director of the Touchstone Diabetes Center at the University of Texas Southwestern Medical Center in Dallas. PhD obtained at the Biocenter of the University of Basel, Switzerland, post-doctoral fellow at the Whitehead Institute at MIT in Cambridge, MA. Throughout his career, he has maintained an interest in processes related to cellular and systemic energy homeostasis. Current efforts in his laboratory are focused on the identification and physiological characterization of novel proteins that serve as potential links between the adipocyte, kidney, liver, the pancreatic beta cell and the processes of whole body energy homeostasis and inflammation.

Facts Regarding Diabetes:

- An estimated **30.3 million people** of all ages—or 9.4% of the **U.S.** population—had diabetes in 2015.
- This total included 30.2 million adults aged 18 years or older (12.2% of all U.S. adults), of which 7.2 million (23.8%) were not aware of or did not report having diabetes.
- The percentage of adults with diabetes increases with age, reaching a high of **25.2% among those aged 65 years or older**.
- Compared to non-Hispanic whites, the age-adjusted prevalence of diagnosed and undiagnosed diabetes was higher among Asians, non-Hispanic blacks, and Hispanics during 2011–2014.
- **Prevalence varied significantly by education level**, which is an indicator of socioeconomic status.
- An estimated **33.9% of U.S. adults** aged 18 years or older (84.1 million people) **have prediabetes**, based on their fasting glucose or A1C level. Nearly **half (48.3%) of adults aged 65 years or older have prediabetes**.
- The total direct and indirect estimated cost of diagnosed diabetes in the United States in 2012 was **\$245 billion**.
- Average medical expenditures for people with diagnosed diabetes were about **\$13,700 per year**. About \$7,900 of this amount was attributed to diabetes.⁶
- After adjusting for age group and sex, average **medical expenditures** among people with diagnosed diabetes were **about 2.3 times higher than expenditures for people without diabetes**.

Source: *National Diabetes Statistics Report, 2017*
National Center for Chronic Disease Prevention and Health Promotion
CDC

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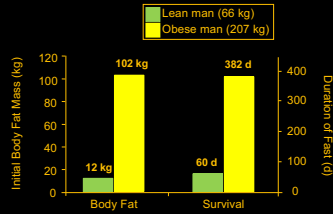
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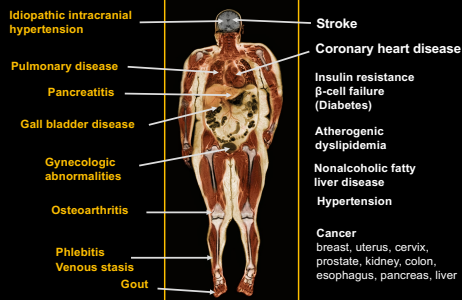
Matrix Biol. in press

Effect of Fat Mass on Survival During Starvation

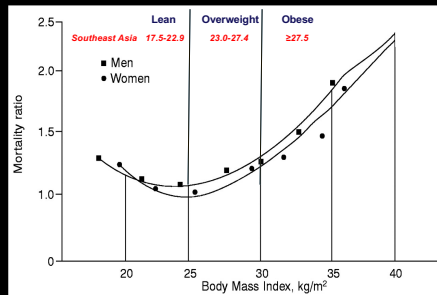


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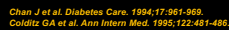
Medical Complications of Obesity

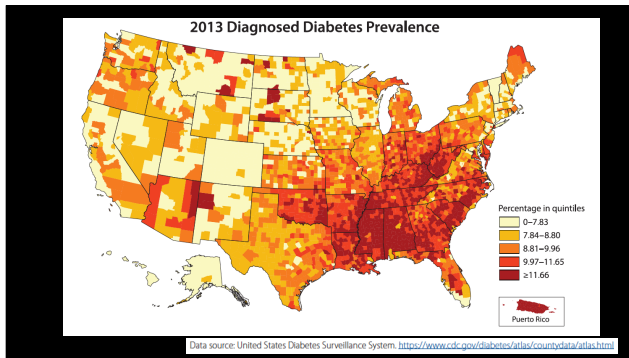


Relation between Mortality and BMI



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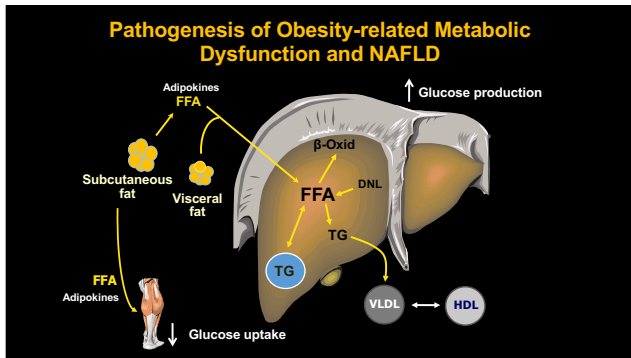
Home > Funding > NIH Categorical Spending

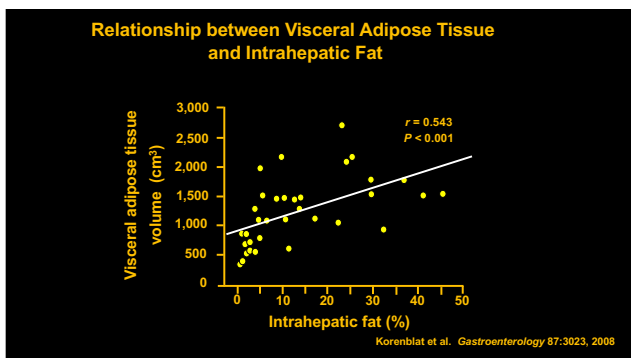
Table Published: May 18, 2018

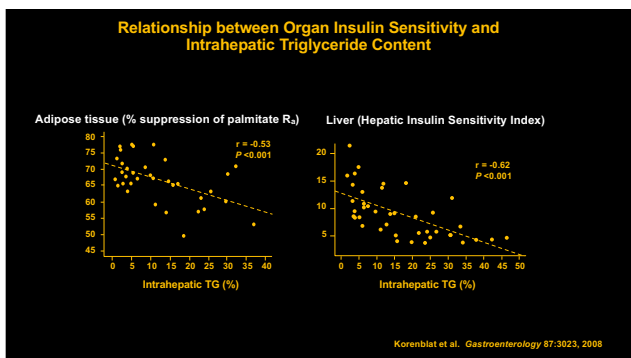
Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)

Research/Disease Areas	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018 Estimated	FY 2019 Estimated	2015 US	2015 US
(Dollars in millions and rounded)	Actual	Actual	Actual	Actual	(Enacted)		Mortality 19/	Prevalence (Standard Error) 19/
Diabetes &/	\$1,011	\$1,010	\$1,084	\$1,108	\$1,172	\$987	252,806	9.7% (0.22%)

For every \$100 spent on diabetes care, we spend about 30 cts on diabetes research



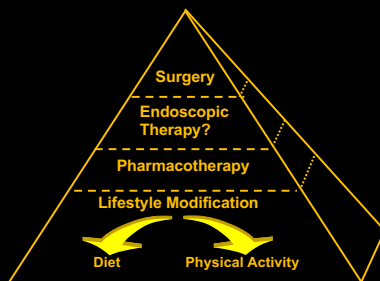




Selected Medications That Can Cause Weight Gain

- Psychotropic medications
 - Tricyclic antidepressants
 - Monoamine oxidase inhibitors
 - Specific SSRIs
 - Atypical antipsychotics
 - Lithium
 - Specific anticonvulsants
- β -adrenergic receptor blockers
 - SSRI=selective serotonin reuptake inhibitor
- Diabetes medications
 - Insulin
 - Sulfonylureas
 - Thiazolidinediones
- Highly active antiretroviral therapy
- Tamoxifen
- Steroid hormones
 - Glucocorticoids
 - Progestational steroids

Obesity Treatment Pyramid



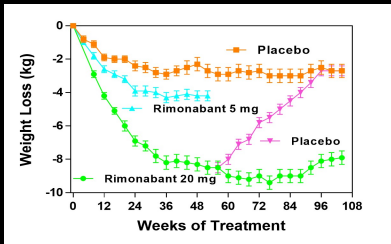
FDA-Approved Drugs for Weight Loss

Year Approved	Generic Name
1947	Desoxyephedrine/methamphetamine
1956	Phenmetrazine
1959	Phentermine
1959	Diethylpropion
1959	Phendimetrazine
1960	Benzphetamine
1972	Fenfluramine Withdrawn 1997
1973	Mazindol
1996	Desfenfluramine Withdrawn 1997
1997	Sibutramine Withdrawn 2010
1999	Orlistat
2012	Phentermine-Topiramate
2013	Lorcaserin
2014	Bupropion-Naltrexone
2015	Liraglutide

5 currently approved by the Food and Drug Administration (FDA) for long-term use:

bupropion-naltrexone (Contrave)
liraglutide (Saxenda)
lorcaserin (Belviq)
orlistat (Xenical)
phentermine-topiramate (Qsymia)

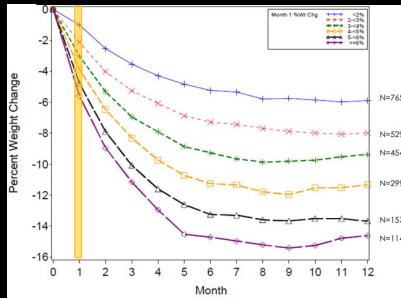
Body Weight Is a Homeostatically Regulated System in Humans



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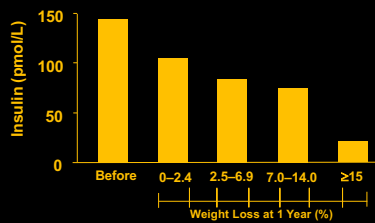
*Rimonabant withdrawn from market.

Intensive Lifestyle Intervention-induced Weight Loss at 1 Month Predicts Weight Loss at 1 Year (Look AHEAD)

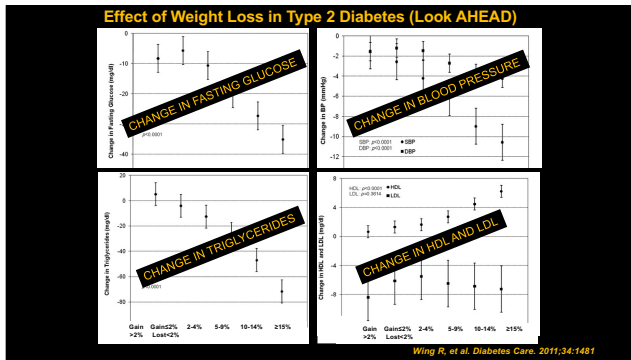


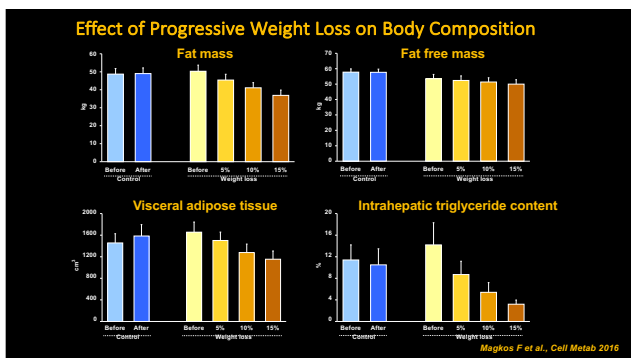
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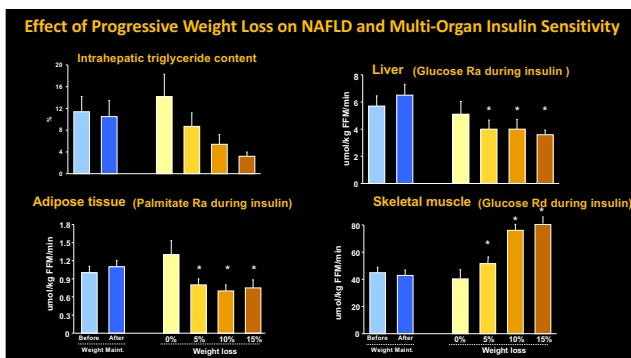
Insulin Sensitivity Improves With Weight Loss in Patients With Type 2 Diabetes

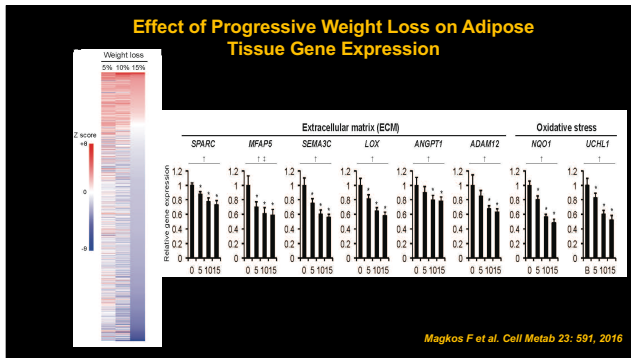


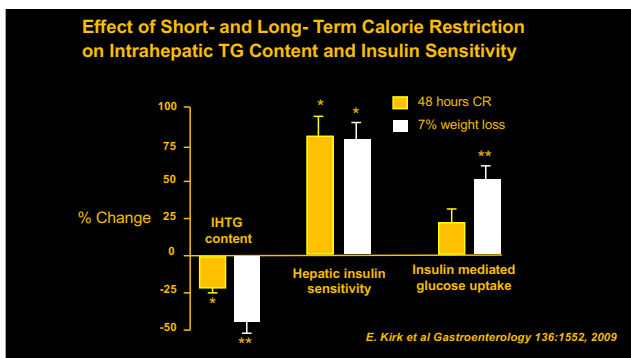
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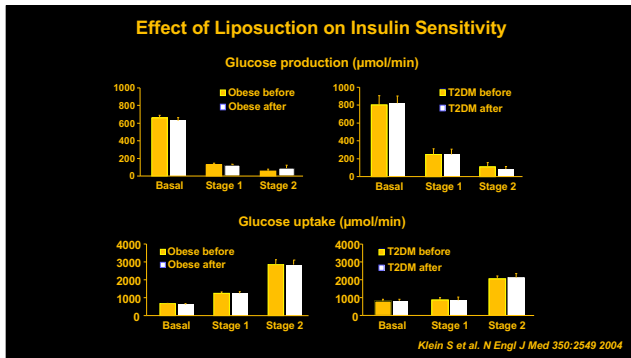


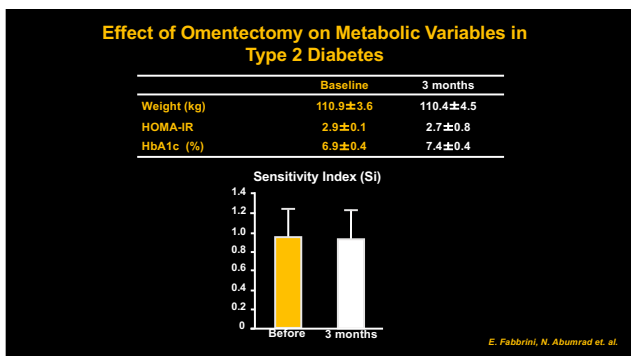


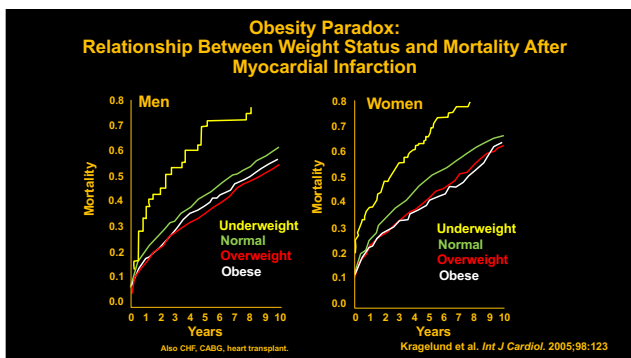
Effect of liposuction on CHD risk factors

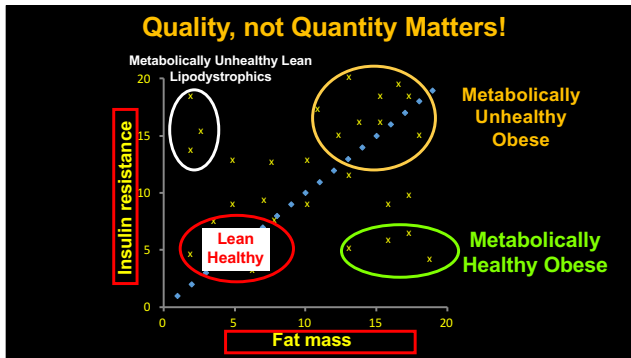
	Obese normal OGT		Obese diabetes	
	Before	After	Before	After
Waist circumference	108±5	94±3*	119±4	107±3*
Systolic BP	119±5	124±4	132±4	137±6
Diastolic BP	70±3	65±4	73±3	68±4
Plasma glucose	89±1	90±2	121±15	123±15
Plasma insulin	11±3	9±2	15±2	14±3
Triglycerides	151±28	121±21	162±19	173±24
Total cholesterol	189±12	174±13	160±9	157±10
LDL cholesterol	113±9	110±11	82±7	80±11
HDL cholesterol	45±8	41±9	44±3	43±3

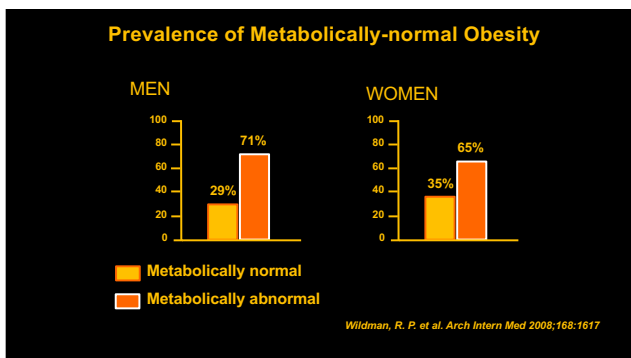
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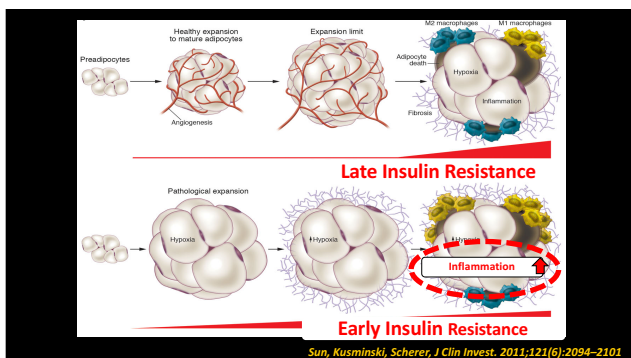


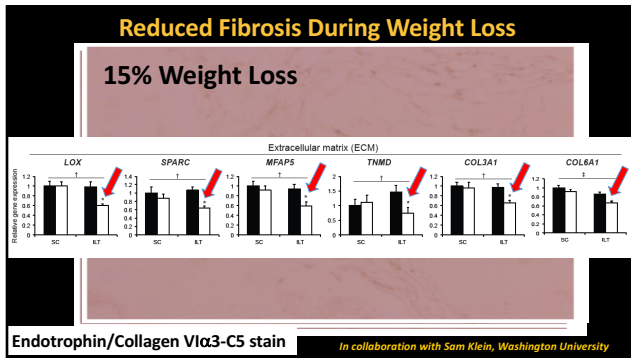


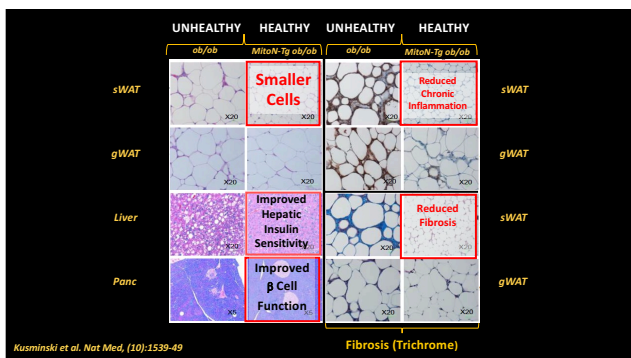


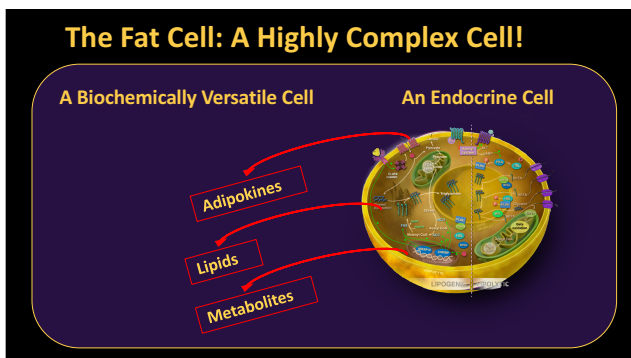


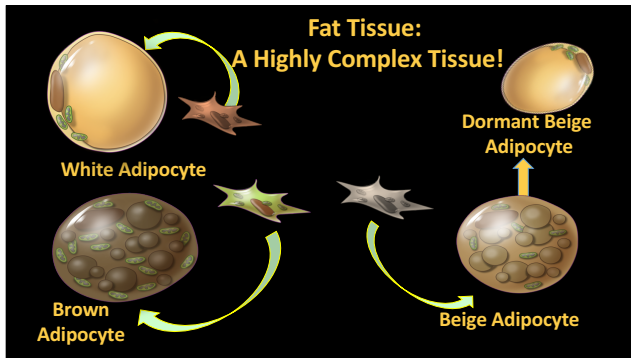


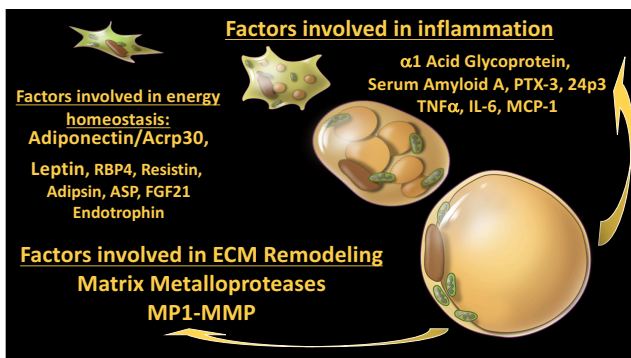


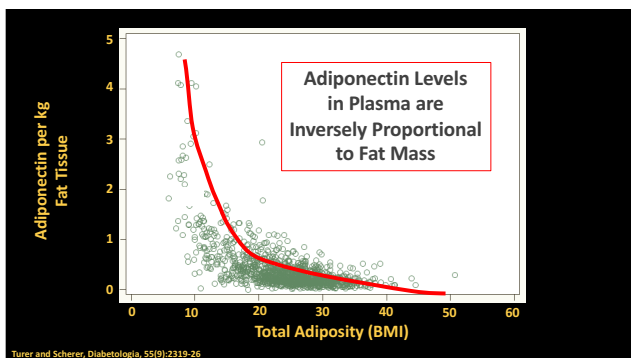


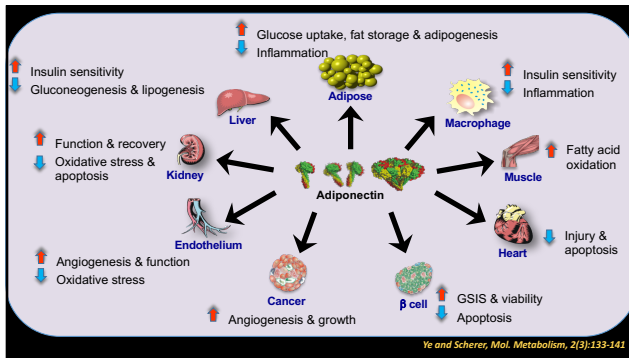












Adiponectin has taught us that a fat-derived factor can be:

- Anti-Apoptotic (Cardiac Myocytes, β Cells, Podocytes)
- Pro-Angiogenic
- Anti-Atherogenic
- Anti-Inflammatory
- Anti-Fibrotic
- Pro-Adipogenic
- Cause Improvements in Liver Insulin Sensitivity

Ceramide Lowering!

Amyloid precursor protein (APP) is elevated in adipocytes upon onset of obesity

Amyloid Precursor Protein Expression Is Upregulated in Adipocytes in Obesity

Yong-Ho Lee¹, William G. Tharp¹, Rhonda L. Maple¹, Saraswathy Nair², Paska A. Permana¹
and Richard E. Pratley¹

The aim of this study was to determine whether amyloid precursor protein (APP) is expressed in human adipose tissue, dysregulated in obesity, and related to insulin resistance and inflammation. APP expression was examined by microarray expression profiling of subcutaneous abdominal adipocytes (SAC) and cultured preadipocytes from obese and nonobese subjects. Quantitative real-time PCR (qPCR) was performed to confirm differences in APP expression in SAC and to compare APP expression levels in adipose tissue, adipocytes, and stromal vascular cells (SVCs) from subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) specimens. Adipose tissue samples were also examined by western blot and immunofluorescence confocal microscopy. Microarray studies demonstrated that APP mRNA expression levels were higher in SAC (~2.5-fold) and preadipocytes (~1.4) from obese subjects. Real-time PCR confirmed increased APP expression in SAC in a separate group of obese compared with nonobese subjects ($P =$

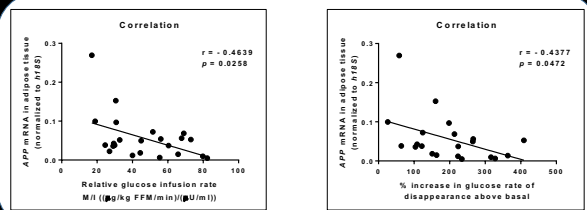
Lee YH, et al. 2008

Amyloid precursor protein (APP) is elevated in adipocytes derived from insulin resistant patients



In collaboration with Sam Klein

APP mRNA is negatively correlated with insulin sensitivity in humans



In collaboration with Sam Klein

Adipocyte-specific APP elimination prevents diet induced obesity and glucose intolerance

