The Contribution of Age-Related Changes in Adiposity to Inflammation and Disease

Derek M. Huffman, PhD
Albert Einstein College of Medicine
Department of Medicine, Division of Endocrinology
Institute for Aging Research
Bronx, NY
Obesity Trends* Among U.S. Adults
(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)
Obesity: The Consequences

- Hypertension
- Stroke
- Heart Disease
- Hyperlipidemia
- Type 2 diabetes
- Cancer
- Gallbladder disease
- Gout
- Eating disorders
- Sleep disorders
- Mood disorders
- Osteoarthritis
Factors that modulate visceral fat accumulation

- Aging
- Gender
- Race
- Diet
- Overall obesity
- Physical Activity
- GH
- IGF-1

- Leptin
- Sympathetic activity
- TZDs/ Metformin
- Glucocorticoids
- Estrogen
- Testosterone
Obesity: The Consequences

Visceral Obesity

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- Cancer
Visceral Fat Distribution: Normal vs Type 2 Diabetes

Normal

Type 2 Diabetes
Visceral obesity and BMI: Association with coronary disease

JAMA, December 2, 1998—Vol 280, No. 21
Visceral fat is an independent predictor of mortality risk

291 Men (56 ± 12yrs)

Adjusted for age, liver fat, SC fat, follow-up time
Visceral obesity and disease in humans: how are they linked?
Adipose tissue macrophages and inflammation
Inflammatory markers associated with increasing visceral adiposity in humans

- **IL-6** (Diamant et al. *JCEM*. 2005)
- **Visfatin** (Fukahara et al *Science* 2005)
- **Leptin** (Ronnemaa et al *Ann Intern Med* 1997)
- **TNFα** (Hishinuma et al *J Stroke Cerebrovasc Dis* 2008)
- **PAI-1** (Giltay et al *Arterioscler Thromb Vasc Biol* 1998)
- **RBP-4** (Kloting et al *Cell Metab* 2007)
- **CRP** (Lemieux et al *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2001)
- **Adiponectin** (Asayama et al *Obesity* 2003)
Aging versus visceral adiposity on systemic inflammation

≤40yr old versus >40yr old

Mean: 28 versus 55 yrs old
Senescence-associated secretory phenotype (SASP)

Yellow = overexpressed; Blue = underexpressed

SASP is conserved among species (humans/mice), tissues, donors/ages SASP is a core, not rigid, phenotype

Judy Campisi, Jean-Philippe Coppe, Chris Patil, Francis Rodier
Visceral fat and insulin resistance: correlation or causation?
Does VF account for the effects of caloric restriction on insulin action in aging rats?

![Bar chart showing body weight (G) for different groups: Young, Old, SC-, Old VF-, Old CR.]

Diabetes; 51:2951, 2002
Does VF account for the effects of caloric restriction on insulin action in aging rats?

YOUNG    OLD SC-    OLD VF-    OLD CR

DoesVFaccountfortheeffectsofcaloricrestrictiononinsulinactioninagingrats?

Diabetes; 51:2951, 2002
'Knock out' of VF prevents diabetes in Zucker diabetic fatty rats

Diabetes; 51:2951, 2002
Does visceral fat modulate lifespan?


CR  n=43
AL  n=56
VF- n=46

*P<0.03 vs AL
Aging *per se* leads to increased visceral fat accrual, macrophage accumulation and sensitivity to nutrients.
Fatty acids provoke PAI-1 transcription levels in cultured macrophages

Kishore and Hawkins et al unpublished data
Importance of nutrients to inflammation

Interaction of Adipose tissue and Nutrients on transcription of inflammatory peptides

Clinical trials are standardized by fasting levels, and are
Underestimating daily transcription of peptides!
Differential response of fat depots to nutrients

A) Resistin
B) PAI-1
C) Angiotensinogen
D) Leptin
E) IL-6
F) TNF-α

DIABETES, VOL. 54, MARCH 2005
Aging *per se* increases the susceptibility of visceral fat to nutrients

* *p*<0.01 vs. all others. #*p*<0.01 vs. age-matched nutrients. **p*<0.01 vs. Young Nutrients

Enhanced activation of a “nutrient-sensing” pathway with age contributes to insulin resistance

Francine H. Einstein,*1 Sigal Fishman,* Jeffery Bamman,* Reid F. Thompson,* Derek M. Huffman,* Gil Atzmon,* Nir Barzilai,*1,1 and Radhika H. Muzumdar*8

**FASEB J.** 22, 3450–3457 (2008)
Aging *per se* in rats is associated with increased macrophage infiltration into fat

*unpublished data*
Treatments: Behavioral strategies

- **Exercise and diet** to promote loss of visceral adiposity

![Image of baseline and post 1 year comparison of visceral fat area and BMI](Image)

- **Exercise *per se*** is anti-inflammatory and may diminish WAT inflammation (Viera et al Cytokine 2009)
Pharmacologic strategies

• **CCR2 antagonists:** limits macrophage infiltration and improves inflammation and insulin resistance in mice (*Weisberg et al J Clin Invest* 2006)

• **Leptin:** selectively depletes VF stores (*Barzilai et al J Clin Invest* 1998)

• **TZD’s:** PPARγ agonists with anti-inflammatory properties, redistribute VF and ectopic fat to subcutaneous fat depot and increase adiponectin
Summary

- A hallmark of aging is an increase in visceral fat

- Visceral fat is more strongly associated with disease than total adiposity or BMI (and potentially mortality)

- The link between visceral fat and disease is causal

- Consideration of the fat x nutrient interaction for provoking inflammatory peptides is often overlooked
Acknowledgments

Einstein
• Nir Barzilai, MD
• Francine H. Einstein, MD
• Gil Atzmon, PhD
• Radhika Muzumdar, MD
• Ilan Gabriely, MD
• Meridith Hawkins, MD
• Preeti Kishore, MD

Barzilai Lab
• Aruna Poduval, MD
• Sigal Fishman, MD
• Temuri Budagov, MS
• Hongqian Liang
• Lingguang Cui

Grant support:
NIH, R01, P01, K08, T32
LWPES
DRTC, AECOM
AFAR
Paul Glenn Foundation
Extra Slides---Not part of presentation (#31-39)
Remaining gaps

• Is there a causal role of VF in humans with age-related diseases? Is it even more severe in humans than rodents?

• What is the contribution of a changing secretory phenotype in aging to inflammation?

• Interaction of nutrients and inflammation with aging in humans?

• What leads to the accrual of macrophages with aging (without obesity)?

• What are the implications of behavioral and pharmacologic strategies to limit visceral fat accrual and adipose-associated inflammation with aging?
Influence of fat depots on adipokine expression and serum levels

Gene Expression by fat depot

Visceral fat removal and serum adipokines

B

Leptin

% expression

120

100

80

60

40

20

0

M

SC

M

SC

TNF-α

Resistin

Fold Increase in Resistin Gene Expression

18

16

14

12

10

8

6

4

2

0

SC

M

R

E

A

TNFα

TNF-α (pg/ml)

200

160

120

80

40

0

C

NO

S

V

C

NO

S

V

IL-6

IL-6 (pg/ml)

250

200

150

100

50

0

†

†

*

†

†

C

NO

S

V

DIABETES, VOL. 51, OCTOBER 2002

Future directions and recommendations

-Human studies should consider analyzing both basal and stimulated (nutrients) circulating inflammatory markers

- Contribution of senescent cells with aging to the inflammatory profile from fat

-Human studies should also consider alternatives to BMI alone when analyzing disease risk (waist circumference, waist-to-hip ratio, waist-to-height, etc)

-Clinical evaluation/progress should emphasize a reduction in waist circumference for patients at risk

-Many questions remain regarding the long-term effects of diet (quality & quantity) and physical activity with aging on macrophage content and activation
Classic versus alternative activation of macrophages

Importance of Macrophages

Ablation of CD11c-Positive Cells Normalizes Insulin Sensitivity in Obese Insulin Resistant Animals

Cell Metabolism 8, 301–309, October 8, 2008
Waist-to-hip ratio trumps BMI for mortality risk in the elderly

Men and Women >75 yrs (mean age ~81yrs)

Greater risk with higher WHR

Subcutaneous fat and metabolic disease

Before Liposuction

After Liposuction

Visceral fat %
of BW (g)

G

Fold induction of 5 min over base level

Body fat distribution: 101