Assessing the Relationship Between Telomere Length and Adipose Tissue Distribution

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Background

- A telomere is a region of repetitive nucleotide sequences at each end of a chromosome which protects the end of the chromosome from deterioration.
- Telomere shortening, a surrogate marker of cellular aging, may accelerate from the inflammatory stressors of obesity.
- The association between adipose tissue depots and telomere length is unknown.

Objectives

- Analyze the association between telomere length and patterns of adipose tissue deposition
- Explore possible mechanisms underlying individual variations in adipose tissue deposition.
- Expand our understanding of the biology of cellular aging

Methods

STUDY POPULATION:
- 2551 participants in the Dallas Heart Study
- Telomere and adiposity data collected between 2007-2009
- 59% Women, 48% Black, 35% Caucasian, 15% Hispanic
- Mean age: 51 years
- Age>60: 23.4%
- Mean BMI: 29.6 kg/m^2

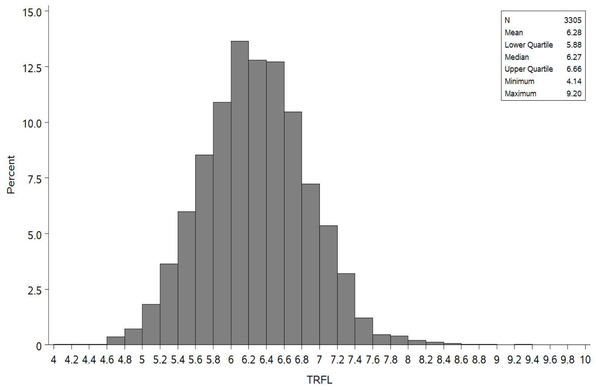
EXPOSURE VARIABLE:
- Peripheral Leukocyte Telomere Length (LTL) measured as total restriction fragment length (TRFL) in kilobases

OUTCOME VARIABLES:
- Visceral Adipose Tissue Mass (VAT)
- Subcutaneous Adipose Tissue Mass (SAT)
- Lower Body Adipose Tissue Mass (LBP)
- Liver Fat (%)
- Assessed by DEXA and MRI

STATISTICAL ANALYSIS:
- Cross-sectional analysis in both continuous and quartiles
- Adjusted for age, race, and sex
- Sensitivity analysis for interactions of severe obesity (BMI> 35 kg/m^2) and by age binning with groups of <40, 40-50, 50-60, >60 years

Results

DHS-2 Telomere Distribution



TRFL Quartile (kb)	N	Min	Max
1	637	4.14	5.89
2	638	5.9	6.3
3	638	6.3	6.69
4	638	6.69	8.89

Univariate Unadjusted Analysis:

Continuous Variables

Variable	Quartile 1 (shortest TRFL)	Quartile 2	Quartile 3	Quartile 4 (longest TRFL)	p
Age (years)	55	51	50	49	<.0001*
VFAT Mass (kg)	2.4	2.37	2.32	2.21	0.003*
SAT Mass (kg)	29.4	30.3	29.7	30.3	0.31
Lower Fat Mass (kg)	10.3	10.4	10.4	10.9	0.02*
Liver Fat Mass (%)	2.5	3.5	2.9	3	0.24
BMI (kg/m^2)	29.4	29.7	29.9	29.7	0.34
Waist:Hip	0.9	0.89	0.88	0.88	0.0002*
Systolic BP (mmHg)	130.6	130.3	128.3	128.3	0.0006*
GFR (mL/min)	90.8	93.8	93.1	94.3	0.02*
Physical Activity (steps)	25	28.14	28.71	32.06	0.0001*

Categorical Variables

Group	Q1	Q2	Q3	Q4	p
Male	45%	40%	44%	35%	.002*
White	37%	38%	35%	32%	.017*
HTN	59%	52%	47%	45%	<.0001*
DM	17%	17%	15%	13%	.022*
Low HDL	69%	68%	67%	65%	.17
Smoker	27%	22%	20%	21%	.003*
Statin Use	22%	18%	18%	16%	.009*

Multivariable-Adjusted Regression Analysis:

Continuous – Standardized β coefficients

	Unadjusted		Adjusted‡	
Variable	Beta	p	Beta	p
VAT	-0.072	0.0002*	0.009	0.6
SAT	0.021	0.29	0.016	0.38
Lower Fat	0.048	0.02*	0.024	0.19
Liver Fat	0.03	0.41	0.032	0.4

Quartile – Standardized β coefficients‡

Variable	Q2 Beta	Q2 p	Q3 Beta	Q3 p	Q4 Beta	Q4 p
VAT	-0.016	0.46	0.024	0.27	0.018	0.41
SAT	-0.024	0.29	-0.003	0.9	-0.017	0.45
Lower Fat	-0.027	0.21	-0.024	0.27	-0.025	0.24
Liver Fat	-0.079	0.13	0.062	0.21	-0.011	0.82

‡Model adjusted for age + gender

Standardized β coefficients = estimated unit change in 1-SD of the log-transformed variable for a 1-SD increase in the telomere parameter.

p-values are noted as significant before (*) correction for multiple comparisons: * $p<0.05$

Discussion

Novel findings:
- Short LTL is associated with pathogenic patterns of adipose distribution
  - high VAT and low LBF
  - These associations are confounded by the linkage of LTL and age

Potential mechanisms:
- Increased inflammatory stress associated with XS VAT accelerates LTL shortening faster than normal cellular aging. Our analysis suggests this hypothesis is incorrect.

Clinical Implications:
- Cellular aging is likely not independently linked to adipose distribution

Conclusion

- In a large, multi-ethnic sample, there are significant associations between short LTL and higher VAT and lower LBP
- The relationship between short LTL and age and male sex largely explain these associations
- Sensitivity analysis demonstrated no significant interaction term at BMI's corresponding with severe obesity.
- Cellular aging is likely not responsible for the pathogenic distribution of adipose tissue and LTL is a poor predictor of clinically relevant obesity sub-phenotypes.
- Future research is needed to identify the true mechanism causing variation of adipose tissue distribution and should re-evaluate the findings of this study in a longitudinal study design.

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