UCLA AMDCC

You can't get old and eat fat

Willa Hsueh, M.D.

Susanne Nicholas, M.D. Ph.D.

Alan Collins, Ph.D.

Rajendra Tangirala, Ph.D.

Jake Lusis, Ph.D.

Richard Davis, Ph.D.

Larry Castellani, Ph.D.

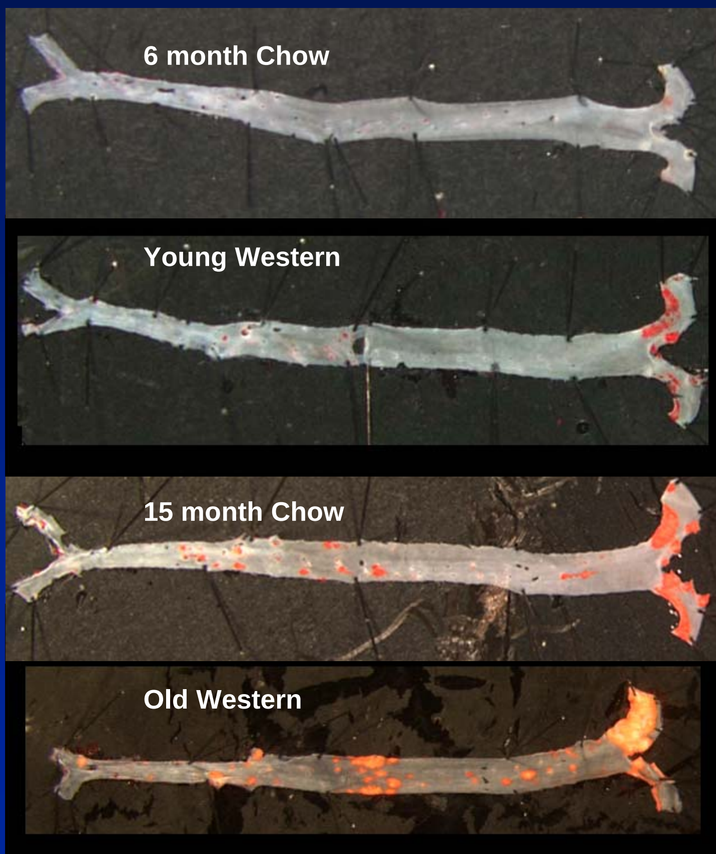
Models of Diabetes or Insulin Resistance Accelerated Atherosclerosis

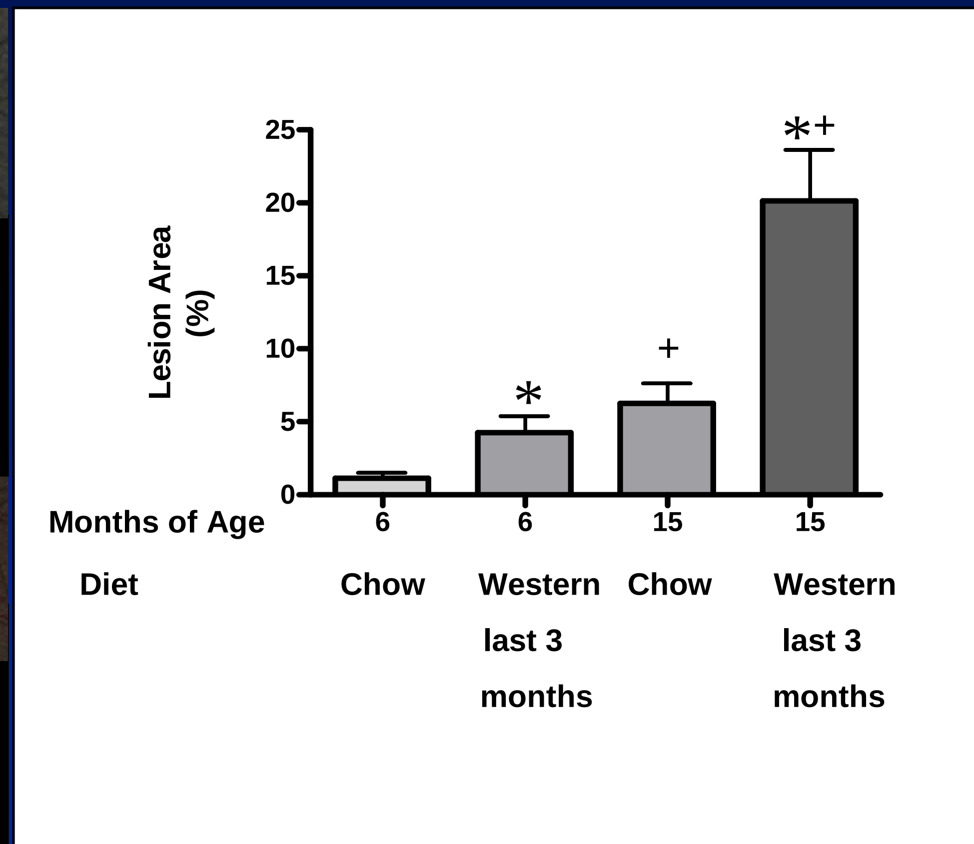
- Angiotensin II infusion
- Congenic strains
- Apolipoprotein AII transgenic
- Skeletal muscle PPARg KO
- Older mouse: high fat diet challenge

Experimental Protocol

Age at start of Protocol	3 Months	Atherosclerosis
(Young) 3 Months ⟶	Western Diet:	Fatty Streaks
(Elderly) 10-12 months	Western Diet:	Advanced Lesions

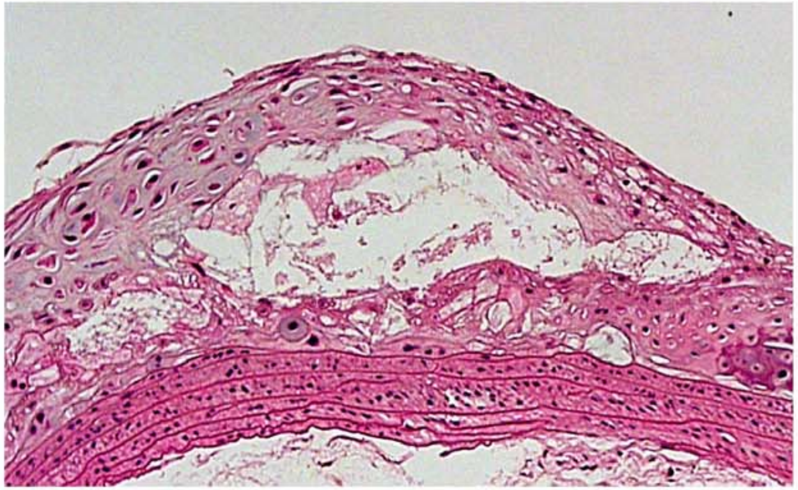
Age Impacts on Vascular Response to Western Diet



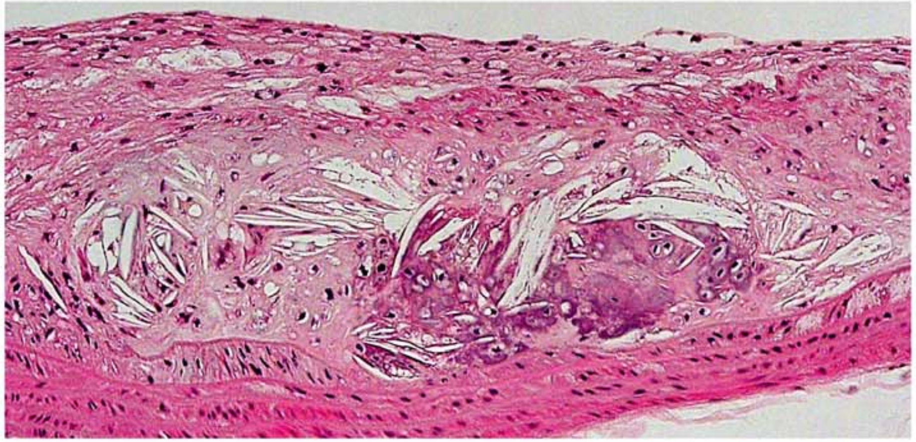


Western Diet Administered to Aged $LDL^{-/-}$ Mice Results in Advanced Atherosclerotic Lesions

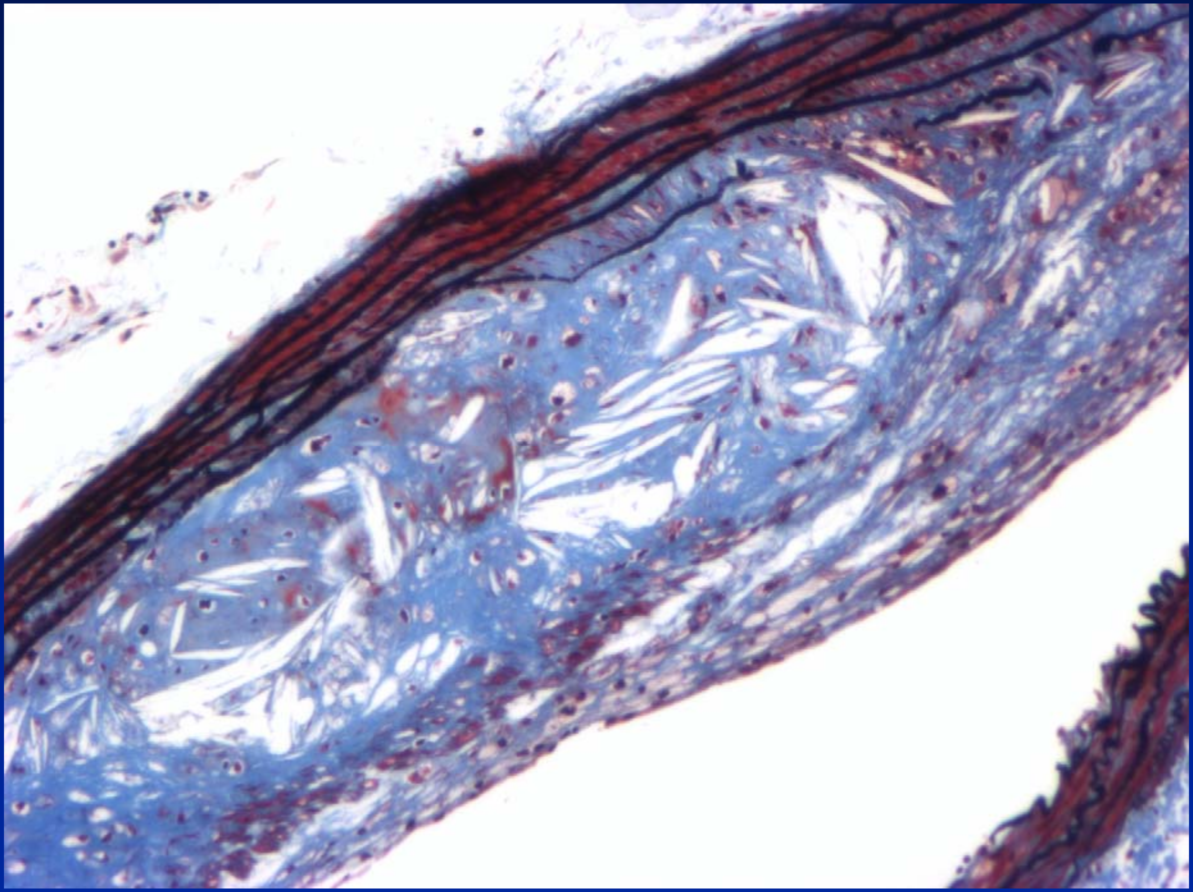
Necrotic Lipid Core



Cholesterol Clefts



Massons Trichrome Stained Section of an Advanced Lesion From the Old LDLR$^{-/-}$ Mice on Western Diet

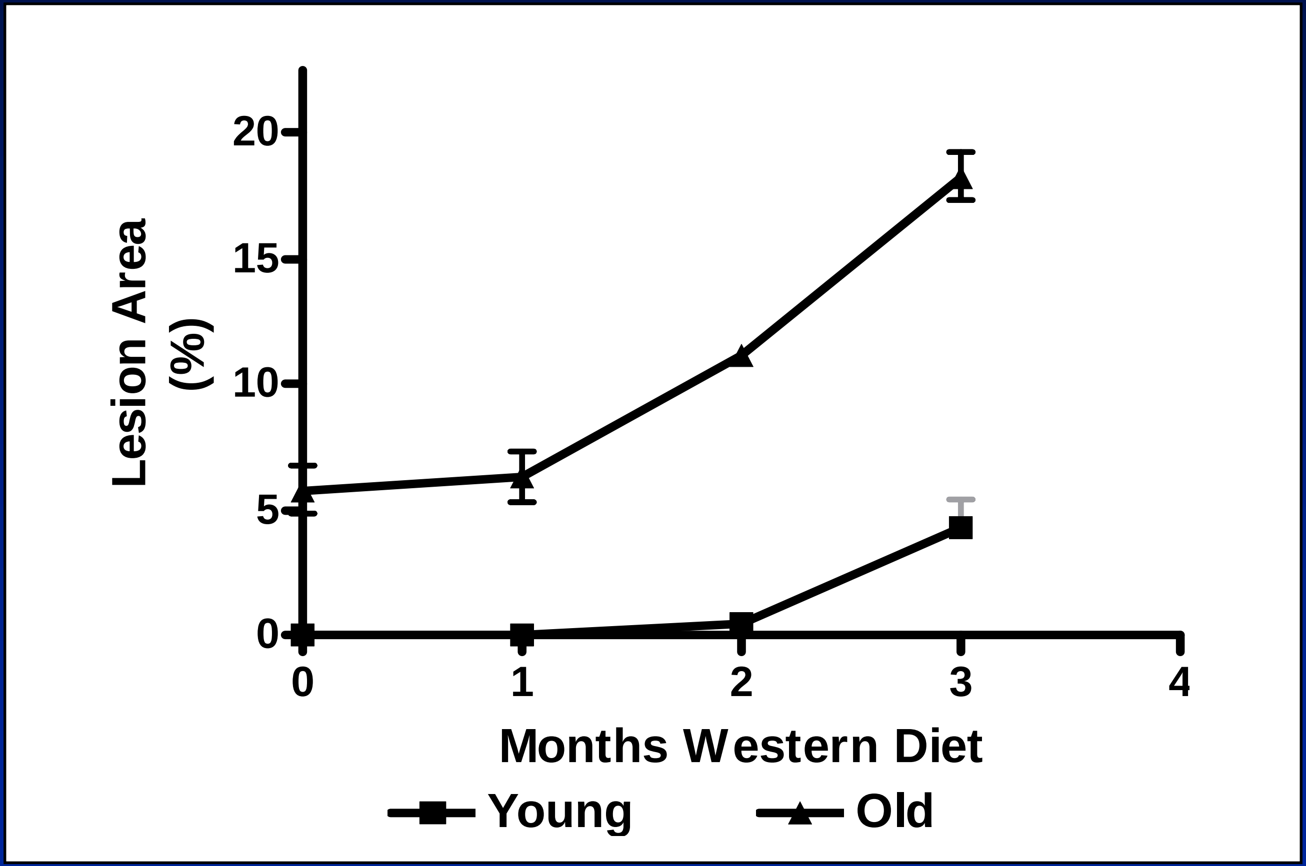


Lesion Complexity Score in LDLR-/- Mice

Young	6%
Elderly	90%

Defined as the percentage of lesions exhibiting necrotic lipid cores, cholesterol clefts, fibrous caps, etc. of the total lesions

Atherosclerosis Extent Progresses Faster in Old Vs Young LDLR$^{-/-}$ Mice on Western Diet for 3 Months



Body Weight, Food Consumption and Blood Pressure

	Initial Body Weight (g)	Final Body Weight (g)	Change in Body Weight (g)	Feed Consumption (g/d)	Systolic Blood Pressure (mmHg)
Young LDLR-/-	24±1.1	42±1.5	18	2.5±0.40	101±3
Elderly LDLR-/-	33±1.8*	51±2.3*	18	2.8±0.36	105±5

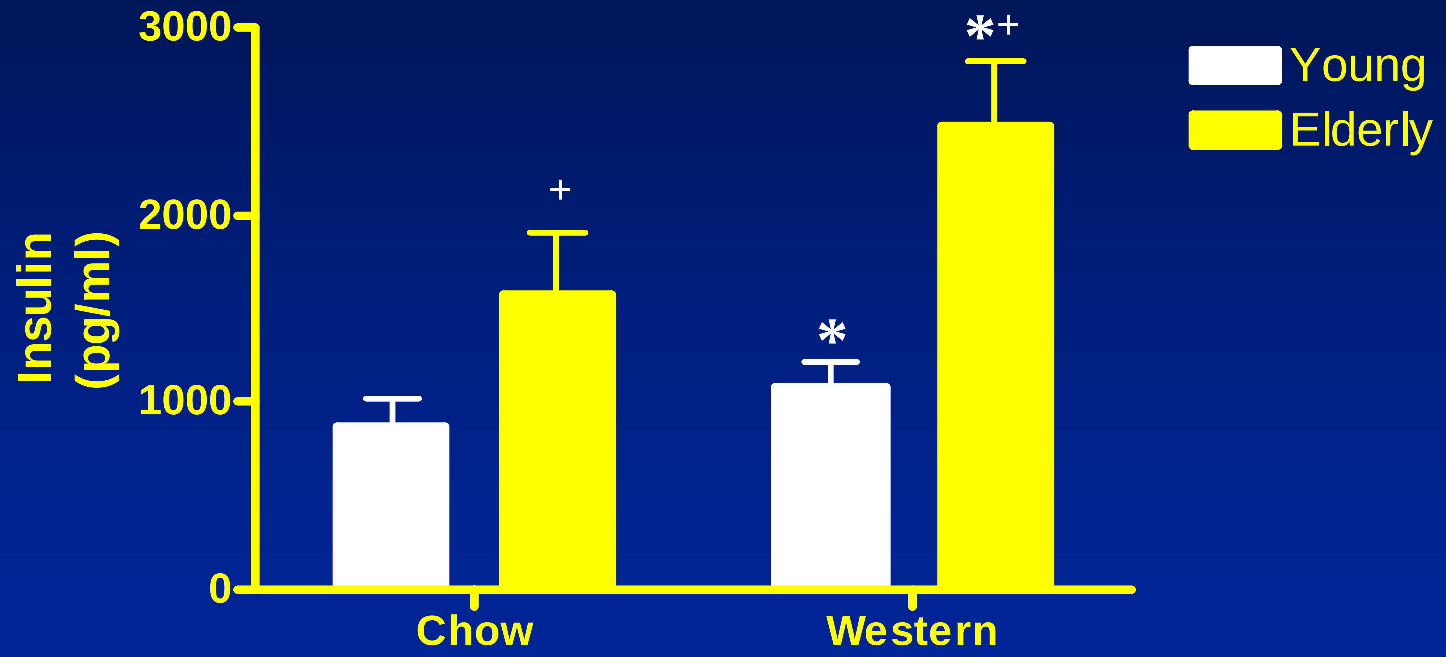
* $p<0.05$

Plasma Metabolic Markers

	Total Cholesterol (mg/dl)	HDL-C (mg/dl)	Triglycerides (mg/dl)	Glucose (mg/dl)	Insulin (pg/ml)
Young LDLR -/-	1842±52	105±8	142±8	285±25	1199±150
Elderly LDLR -/-	1928±154	67±5*	371±60*	423±27*	2609±354*

* $p<0.05$

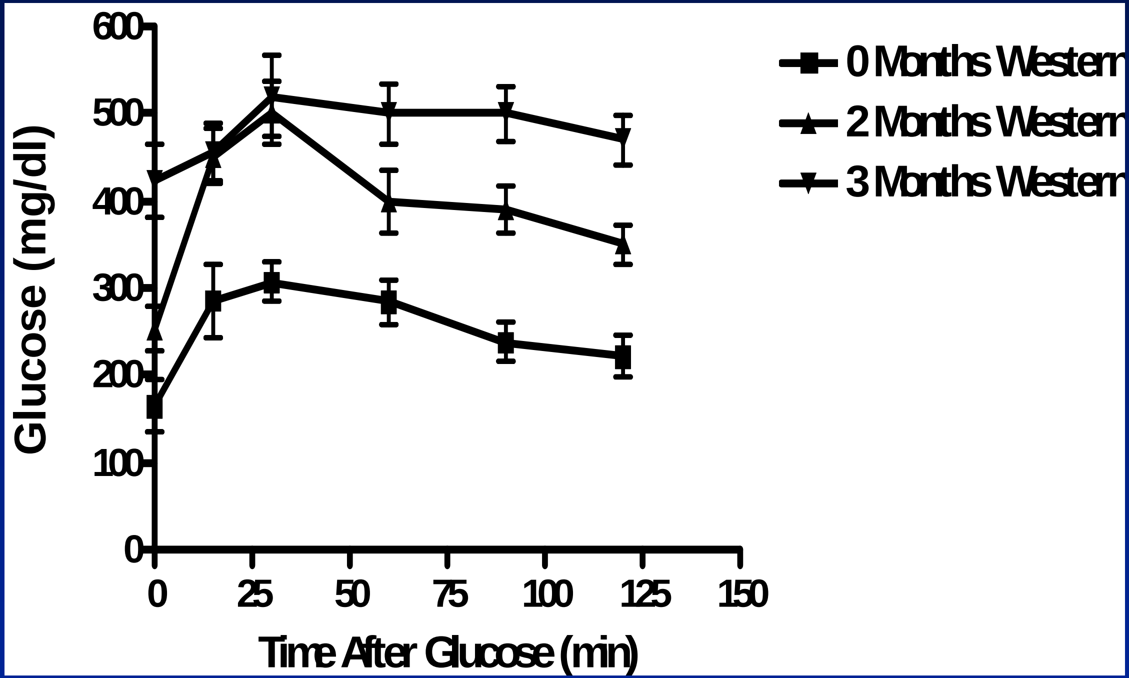
Effects of Age and Diet on Insulin in Male LDLR-/- Mice



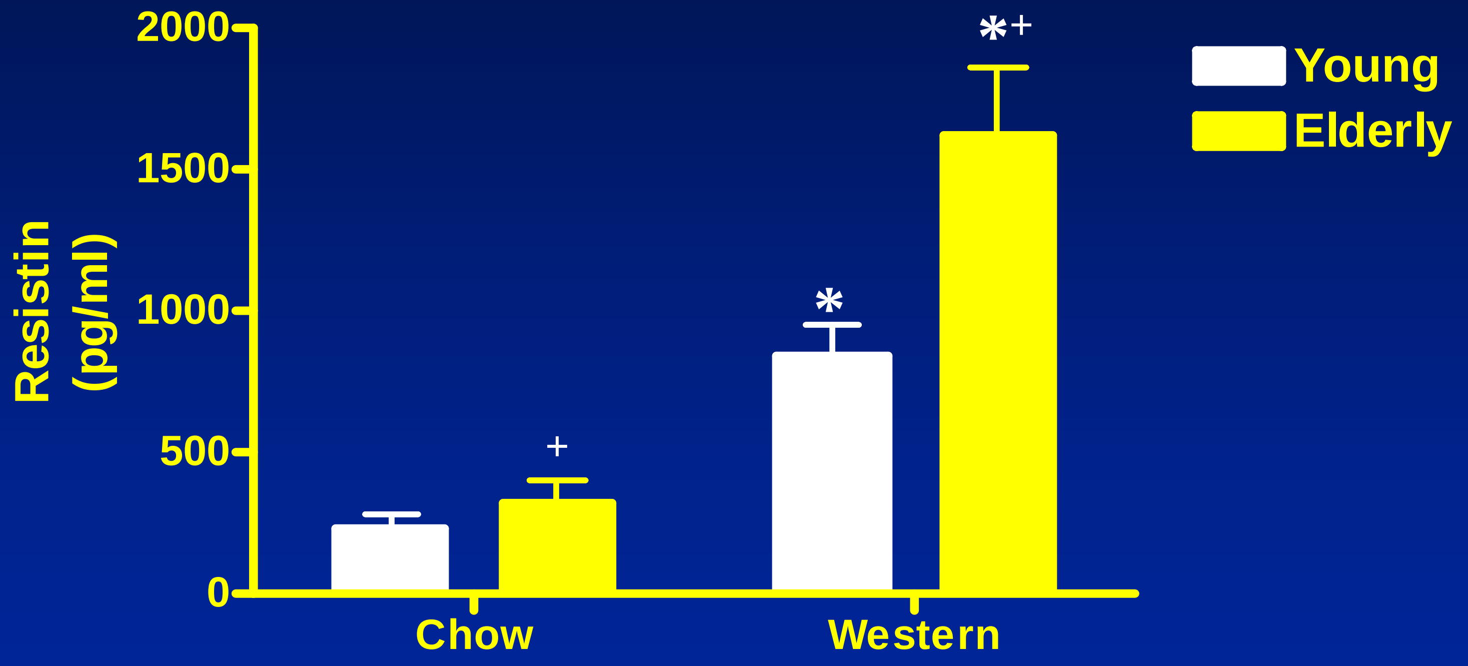
* p<0.05 Western vs chow

+ p<0.05 Elderly vs young

OGTT responses progressively worsen in older LDLR$^{-/-}$ mice from 0-3 months of Western diet



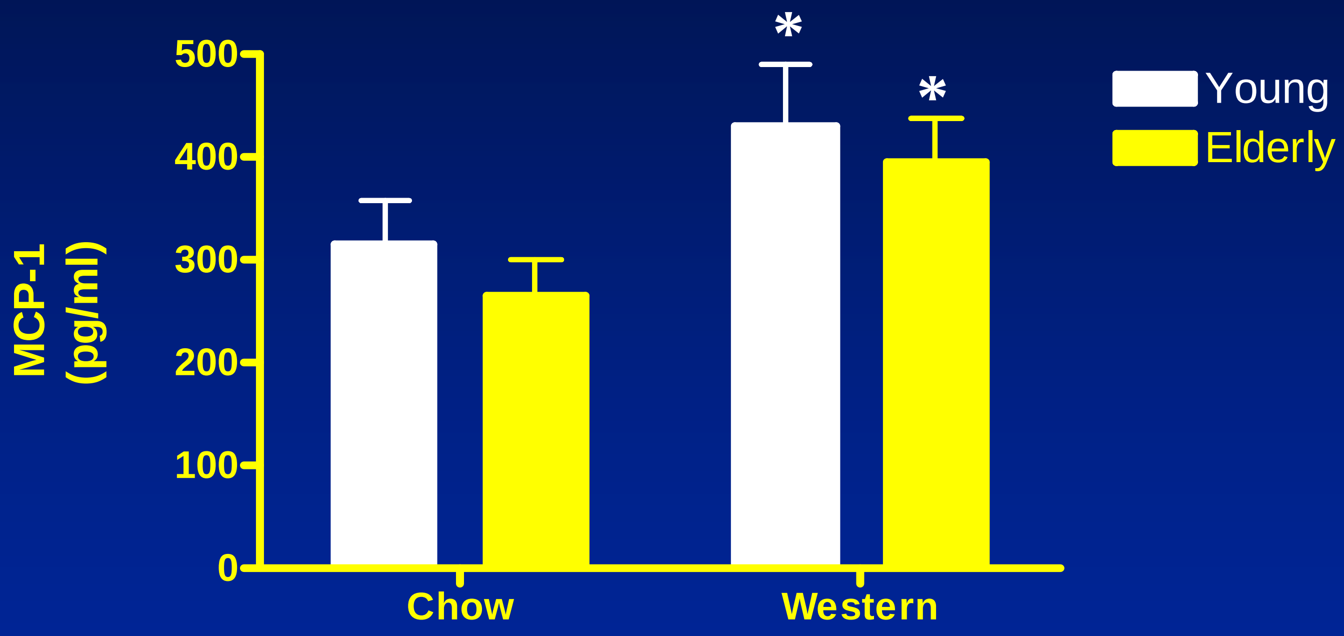
Effects of Age and Diet in Male LDLR-/- Mice



* p<0.05 Western vs chow

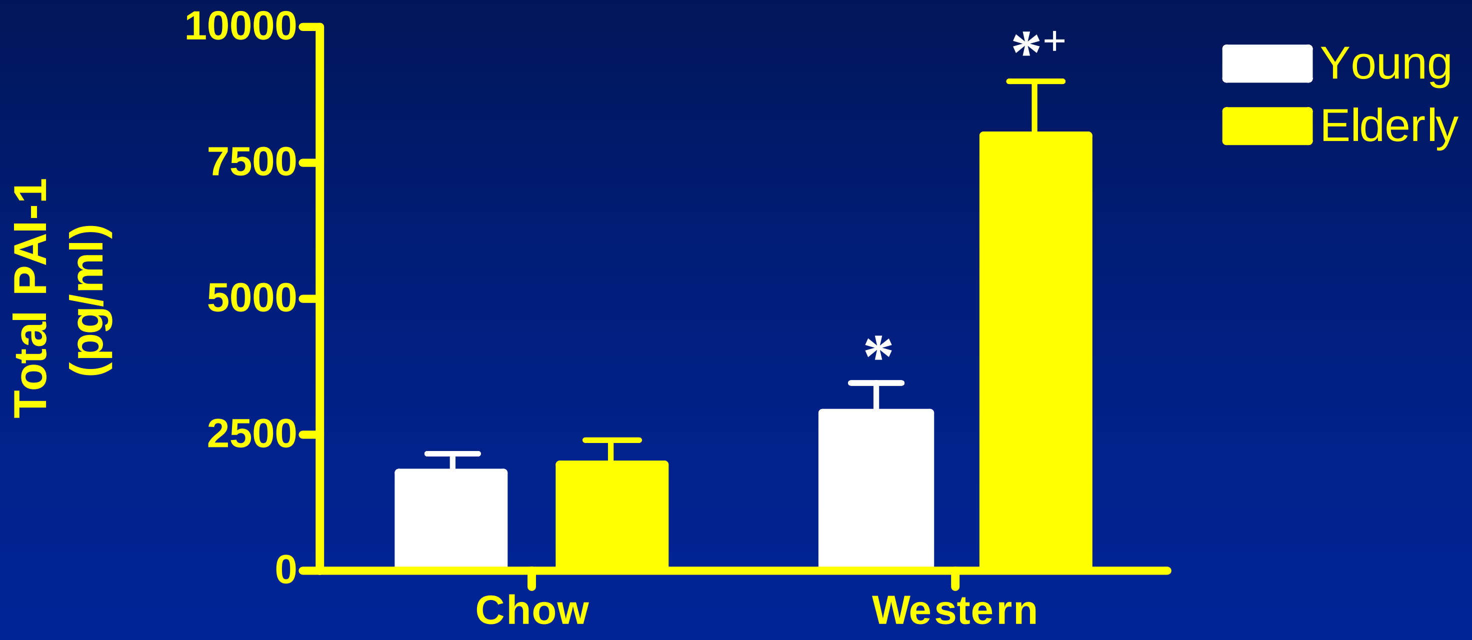
+ p<0.05 Elderly vs young

Effects of Age and Diet in Male LDLR-/- Mice



*** p<0.05 Western vs chow**

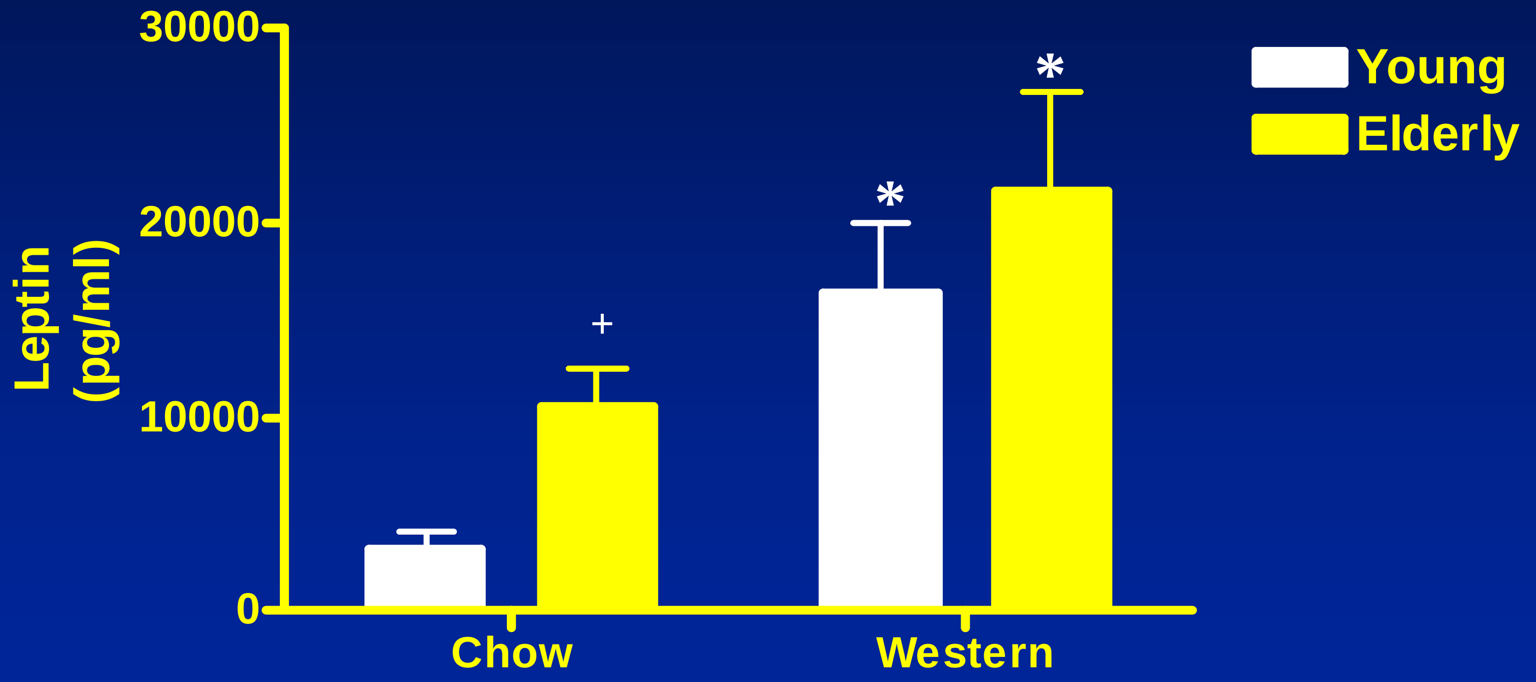
Effects of Age and Diet in Male LDLR-/- Mice



* p<0.05 Western vs chow

+ p<0.05 Elderly vs young

Effects of Age and Diet in Male LDLR-/- Mice



* p<0.05 Western vs chow

+ p<0.05 Elderly vs young

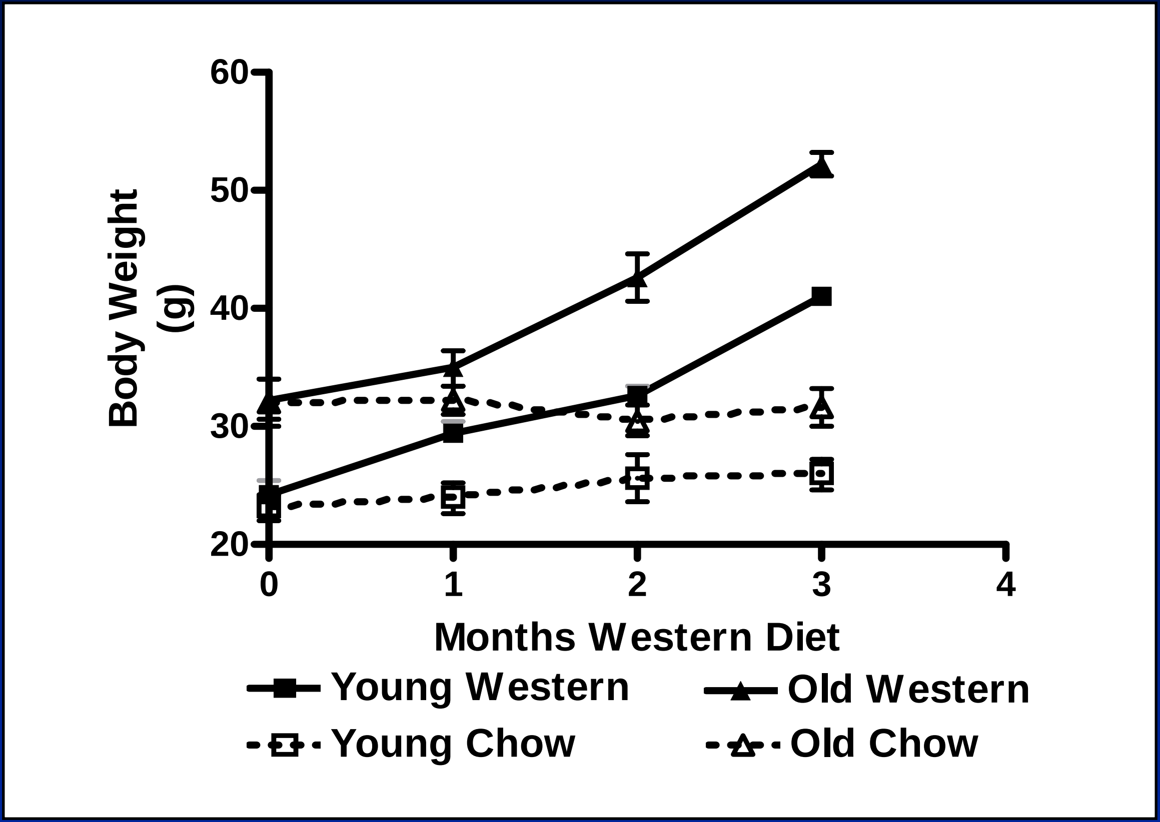
No Differences in Young vs Elderly LDLR$^{-/-}$ Mice

TNF-α

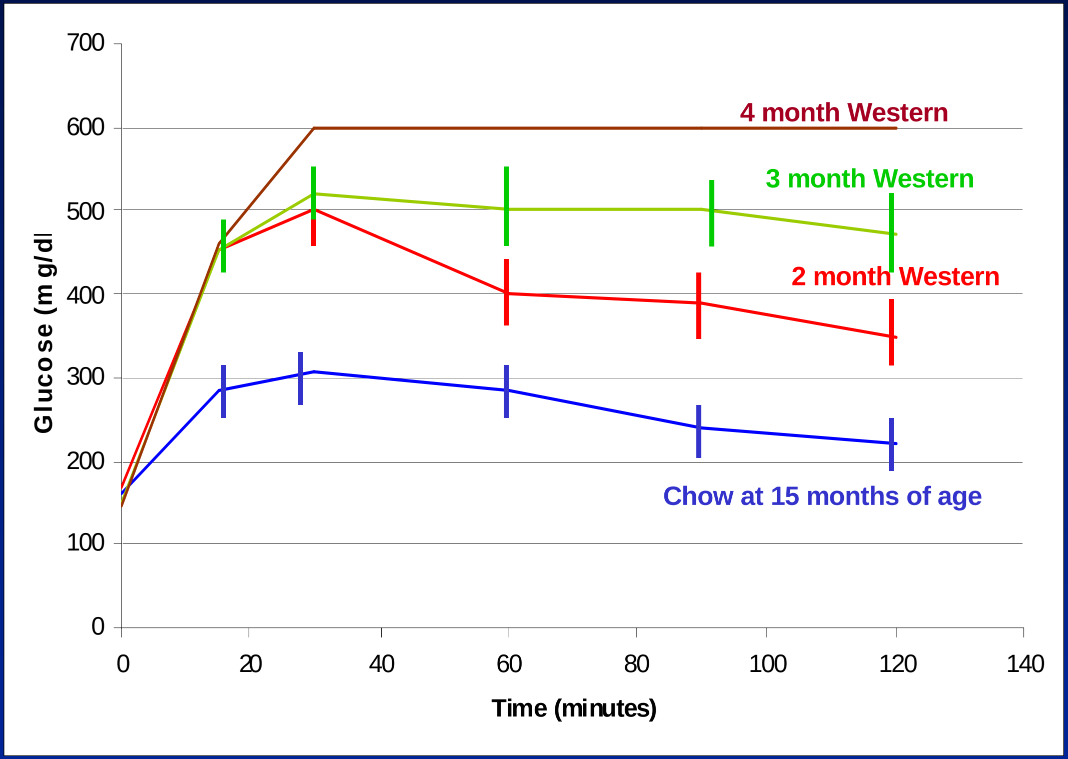
IL-6

Adiponectin

Western Diet Promotes Weight Gain at Similar Rates in Both Young and Old LDLR-/- While There Is No Weight Change on Chow. Older Mice Start About 10 Grams (G) Heavier Than Young Mice



4 month Western diet mice exceeded glucometer reading at >600 mg/dl



Differential Regulation of Oxidative Stress Response Genes in the vasculature in Older Mice to Western and Chow Diet

Oxygen and reactive oxygen species metabolism				
Western Diet				
AccNo	**Description**	**Old/young**	**Young**	**Old**
NM_008161	glutathione peroxidase 3 (Gpx3)	-2.9	2341	808
NM_008162	glutathione peroxidase 4 (Gpx4)	-2.3	4625	1977
NM_008160	glutathione peroxidase 1 (Gpx1)	-2.5	2081	844
NM_013671	superoxide dismutase 2, mitochondrial (Sod2)	-2.3	780	338
NM_009804	catalase 1 (Cas1)	-1.8	4600	2613
NM_010497	isocitrate dehydrogenase 1 (NADP+), soluble (Idh1)	-4.3	173	40
NM_023719	thioredoxin interacting protein (Txnip)	-2.0	459	226
Chow Diet				
NM_023719	thioredoxin interacting protein (Txnip)	5.9	147	872
NM_008160	glutathione peroxidase 1 (Gpx1)	3.6	404	1437
AK021200	ES cells cDNA, RIKEN full-length enriched library, clone:C330014H07:cytochrome b-245, alpha	2.6	2892	7381
NM_030677	glutathione peroxidase 2 (Gpx2)	11.9	22	261
NM_010877	neutrophil cytosolic factor 2 (Ncf2)	2.8	234	664
NM_008162	glutathione peroxidase 4 (Gpx4)	2.2	1440	3167
NM_010497	isocitrate dehydrogenase 1 (NADP+), soluble (Idh1)	14.0	8	105

Western	**NM_011671**	**uncoupling protein 2, mitochondrial (Ucp2)**	**-2.9806**	**875.7**	**293.8**
Chow	NM_011671	uncoupling protein 2, mitochondrial (Ucp2)	8.5431	110.3	942.3
Western	**NM_009155**	**selenoprotein P, plasma, 1 (Sepp1)**	**-1.8077**	**2781**	**1539**
Chow	NM_009155	selenoprotein P, plasma, 1 (Sepp1)	3.8061	604	2298.9

Lipid and Glucose Levels in LDLR$^{-/-}$ Mice With Time

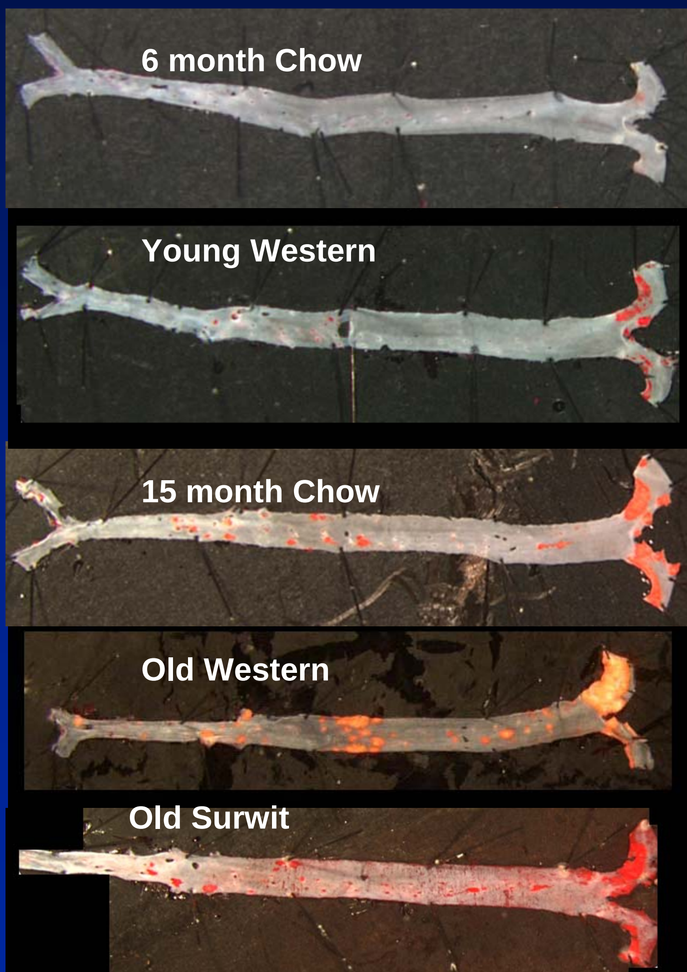
	Total Cholesterol (mg/dl)		Triglycerides (mg/dl)		HDL-cholesterol (mg/dl)		Glucose (mg/dl)	
	Young	Old	Young	Old	Young	Old	Young	Old
Chow	292±15	273±7	122±4	119±18	111±5	90±5	159±15	167±28
1 month Western Diet	583±72	654±82	124±7	157±21	108±2	82±5	190±11	251±26
2 month Western Diet	1307±110	1536±217	157±31	258±64	90±4	74±3	201±9	357±24
3 month Western Diet	1842±52	1928±154	147±11	371±60	105±8	67±5	285±25	423±27

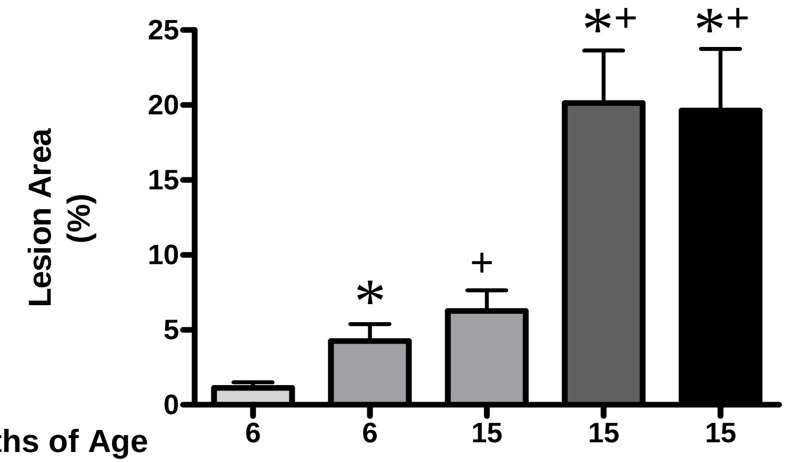
Future Directions

- Use a lower cholesterol diet to distinguish the role Of the metabolic syndrome in atherosclerosis in this model

- Define the role of the inadequate CPX system response in accelerated atherosclerosis

Age Impacts on Vascular Response to Western Diet





Months of Age	6	6	15	15	15
Diet	Chow	Western last 3 months	Chow	Western last 3 months	Surwit last 3 months
Plasma Cholesterol (mg/dl)	292±15	1842±52*	273±7	1928±154*	678±94*

*$p<0.05$ vs Chow Diet

+$p<0.05$ 6 vs 15 months