The Kidney in Aging

Reduced Renal Function (RF) is a Major Cause of Increased Oxidative Stress (OS) and inflammation (Infl) in "Normal" Adults

Is Reduced RF now universal in Aging?

Does OS/Infl Cause Reduced RF now thought to be universal in Aging?

If OS/Infl underlies aging-related diseases, it may be preventable. Thus, ↓RF could and should be treated.

Summary and Conclusions

- **Does everyone get ↓RF as they age? Not all**
- **Are AGEs and OS involved? Yes**
- **Does ↑↑ Infl/ROS/AGEs cause ↓ RF in aging? Yes**
- **What are the sources of oxidants? Exogenous**
- **What are the mechanisms? Infl/ROS formation**
- **How might one prevent or treat ↓ RF in normal adults, prevent or treat the CKD of aging?**
  Reduce ROS/Infl and AGE formation or intake
- **Why does it matter, i.e. why bother to treat?**

The kidney actively excretes and filters AGEs.

***↓RF leads to ↑↑ infl, ↓anti-Oxid reserves, ↑↑ OS and ↑↑ risk of CVD, AD, bone and other aging diseases.**

Age and Kidney Function

The Cleaning Crew Goes on Strike! (Reduced Renal Function)

Luigi Ferrucci MD, PHD
Longitudinal Studies Section
Clinical Research Branch
National Institute of Aging

Importance of Reduced RF in Aging

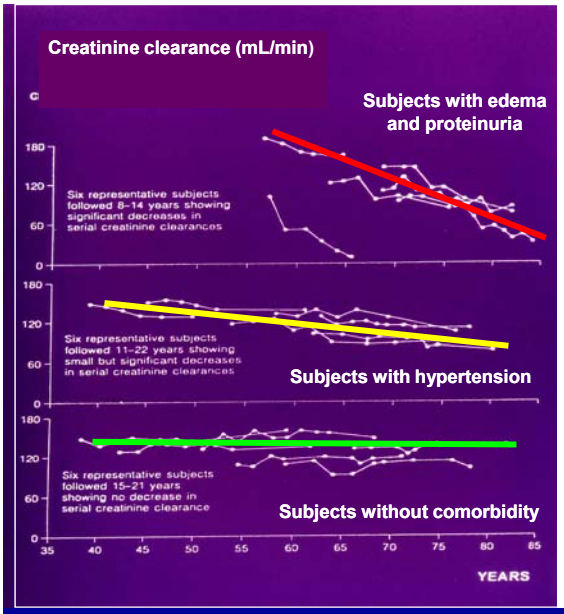
- Aging is an <u>inflammatory condition</u> associated with ↑OS and ↓anti-ox reserves.
- The kidneys are a primary site for the metabolism and excretion of circulating oxidants.
- Decreased RF signals ↑ infl, ↑ OS, and ↓anti-ox reserves; risk factors for acute injuries, aging-related diseases (CVD, AD, etc.). Thus, it should be recognized and treated.
- Decreased RF and OS in adults can be blocked by currently available treatments.

Reduced RF of Aging, Risk Factors

- The risk of developing ↓RF in aging is increased in conditions associated with elevated OS:
  - CVD/atherosclerosis
  - Hypertension
  - Other forms of CKD
- This suggests that those who develop CKD in aging could have increased /InflOS as a major underlying cause (in addition to genetics).
- What is the evidence that RF does or does not decline with aging in normals vs. disease states?

Do All Develop the CKD of Aging?

446 men were studied in the Baltimore Longitudinal Study of Aging

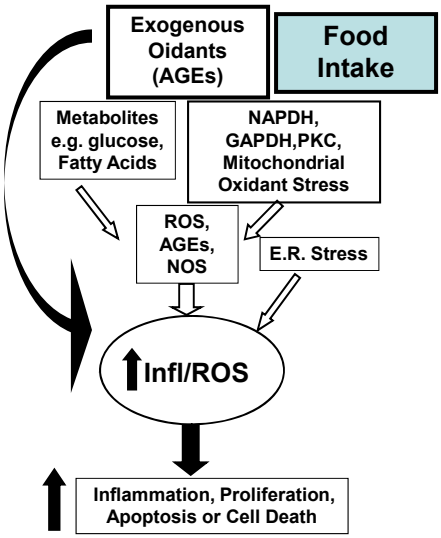


Lindeman RD et al. *J Am Ger Soc* 1985; 33: 278

Reduced RF in Aging (Infl/OS)

- Is increased Infl/OS associated with, or causal of, decreased Renal Function in adults?
  - OS is increased in patients and animals with early and late stages of CKD
    - Late: High serum levels of oxidants (Himmelfarb, etc.)
    - Early: increased urinary excretion of oxidants (Vlassara)
    - Late: decreased oxidant excretion (Vlassara)
    - Decreased antioxidant levels (multiple authors)
  - Decreasing oxidant intake prevents reduced renal function in aging animals (Vlassara)
- What is the Source of the Infl/Oxidants that induce OS?

Sources of Oxidative Stress



The diet is a major source of oxidants in normal adults.

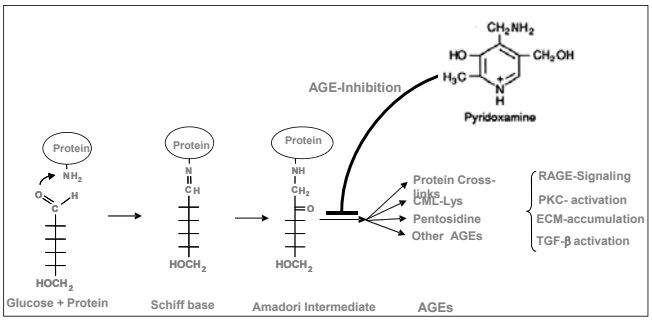
What is the evidence in animals and humans?

Do Oxidants in the Diet Induce OS? Studies in Normal Humans

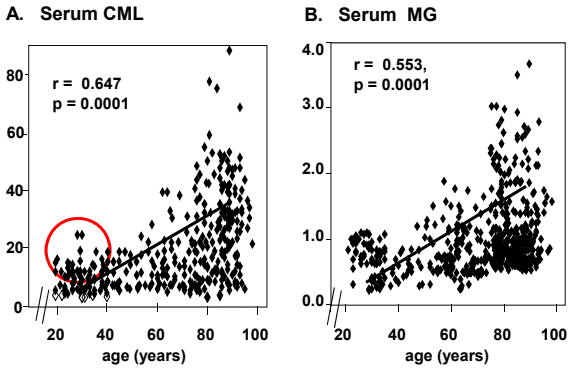
- Are Toxic Oxidants Contained in the Diet Absorbed of Humans? Yes
- Do they Induce OS? Yes
- What is the composition of the oxidants?

What are AGEs or Advanced Glycation Endproducts?

What are they? How do they Form?



Studies in Normal Volunteers

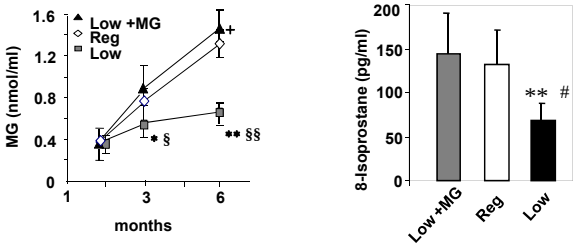


The accumulation starts at an early age.

Are AGEs in the diet the source of the Infl/OS injury in normal aging? Will first show you studies in Mice.

Do AGEs in the Diet Induce OS?

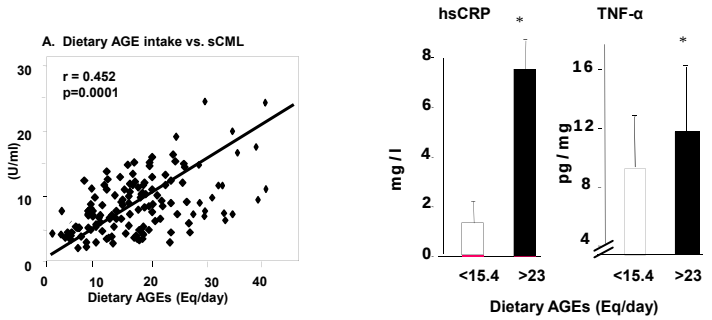
Studies in Mice (Methylglyoxal, MG)



Dietary oxidants (including AGEs) Induce Infl/OS in Mice.

Does this apply to humans?

Relationship between Dietary and Tissue Oxidants in "Normal Adults"



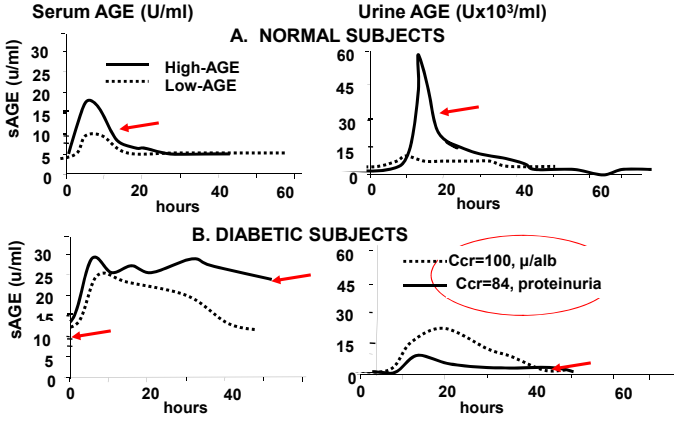
Thus, oxidants (AGEs) in the serum directly correlate with the levels of oxidized lipids, inflammatory mediators (TNF-α) and of overall inflammatory status (hsCRP) in normal adults.

Studies in Normal Volunteers

Do the serum level of AGEs in normals and/or diabetics change how the kidneys deal with dietary oxidants (AGEs)?

Studies in Normals and Diabetics

Serum/urine levels are parallel, high intake leads to persistently high serum and urine normals.



AGE excretion is delayed prior to decreased RF in DM!!

AGE excretion is directly related to intake in nmls & CKD.

Overview of OS/Inflammation

- **AGEs are a major cause of OS/Inflammation**
- **What types of AGEs are there?**
  - **"Toxic oxidants": i.e. MG (methylglyoxal)**
  - **"Less Toxic End products" i.e. CML**
- **The conversion of MG to CML (toxic to less-toxic) is critical to normal oxidant status.**
- **How are AGEs recognized/metabolized in normal subjects and in CKD?**

AGE Receptors

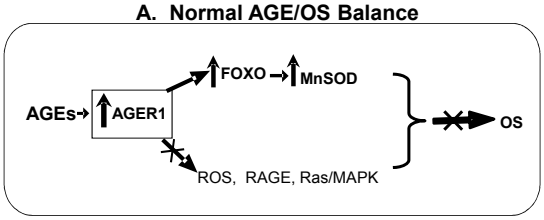
Receptors	Functions
AGE-R1	↓Anti-Oxidant Stress
	↓Inflammatory responses
	↑AGE removal
RAGE TLR4	↑Oxidant Stress
	↑Inflammatory responses

These AGE receptors mediate unique/opposite effects.

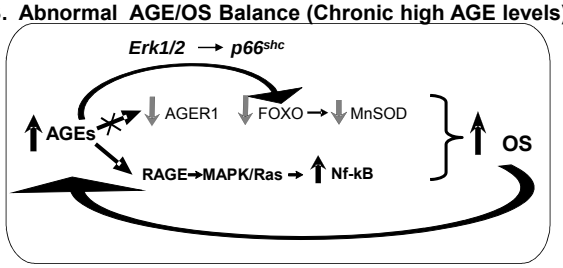
What mechanisms are involved?

AGE/AGE Receptor Interactions

A. Normal AGE/OS Balance



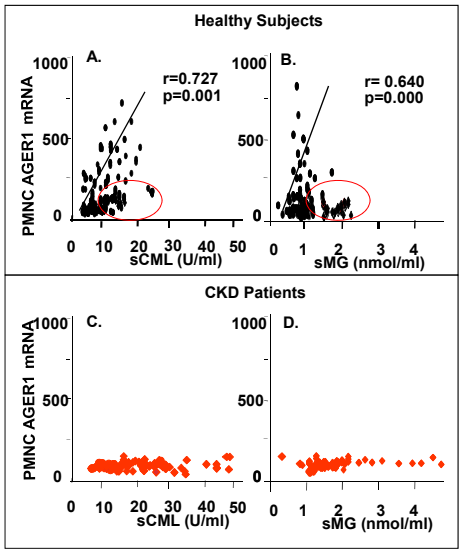
B. Abnormal AGE/OS Balance (Chronic high AGE levels)



Thus, AGER1 is protects from and RAGE promotes Infl/OS.

Do AGER1 levels in CKD patients differ from Normals?

AGER1 levels in Normal Adults and CKD Patients



AGER1 levels ↑ as AGEs levels ↑ in normal adults

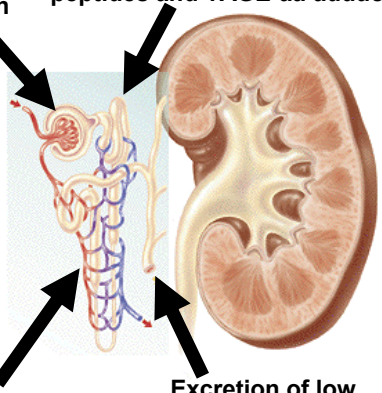
AGER1 is fixed at a low level in all CKD patients. This may explain the high levels of AGEs in CKD.

Therefore, AGER1 reduces AGE levels in normals.
How do the kidneys normally excrete oxidants (AGEs)?

The Kidney and Oxidant Metabolism

Filtration

Uptake/process filtrate with AGE-peptides and ?AGE-aa adducts

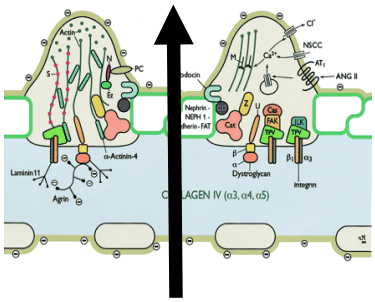


Basal uptake and metabolism of oxidants

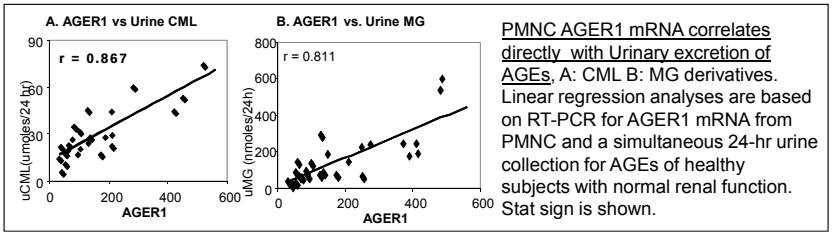
Excretion of low MW AGE-peptides, AGE adducts

Filtrate: <50kDa neutral molecules, including low-MW AGE-peptides

Filtration barrier



Thus, both filtration and basolateral uptake are important routes of oxidant (AGE) metabolism in the kidney and may be affected by baseline ROS.



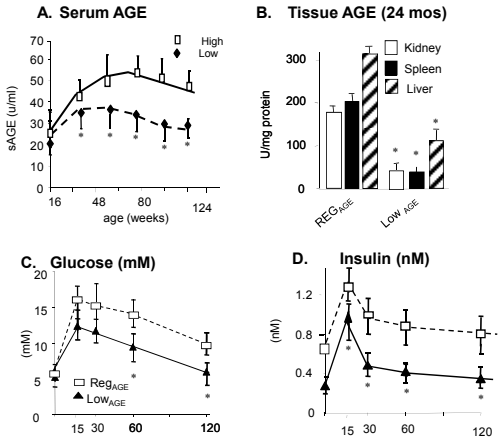
PMNC AGER1 mRNA correlates directly with Urinary excretion of AGEs, A: CML B: MG derivatives. Linear regression analyses are based on RT-PCR for AGER1 mRNA from PMNC and a simultaneous 24-hr urine collection for AGEs of healthy subjects with normal renal function. Stat sign is shown.

Renal Elimination of AGEs

- Filtration of low MW AGE peptides
- Filtration of AGE-modified small peptides
  - Uptake and degradation/detoxification in PCT cells at the luminal side.
  - ??Effect of oxid/anti-oxid balance on tubular fx
- Basolateral Uptake
  - Uptake and degradation/detoxification in PCT cells
  - ??Effect of oxid/anti-oxid balance on tubular fx
- Effects of AGEs on tubular fx may explain why the metabolism of AGEs is decreased in diabetics, prior to a change in sCr.

Effects of excess dietary AGE exposure in Normals

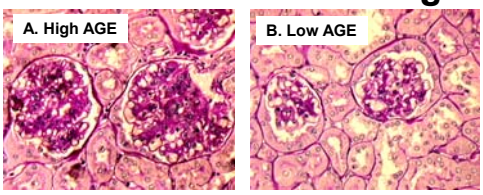
Studies in Mice Fed Low or High AGE Diets

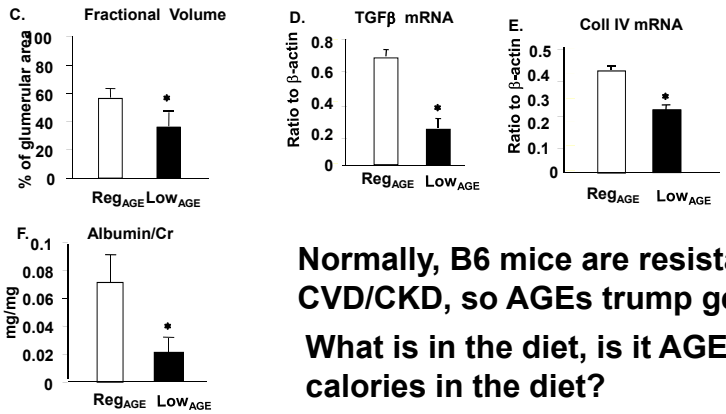


A high AGE-diet increases AGEs in mice, causes insulin resistance, and then frank diabetes.

Is this associated with CKD or CVD?

Renal Lesions after a Low or Regular AGE Diet





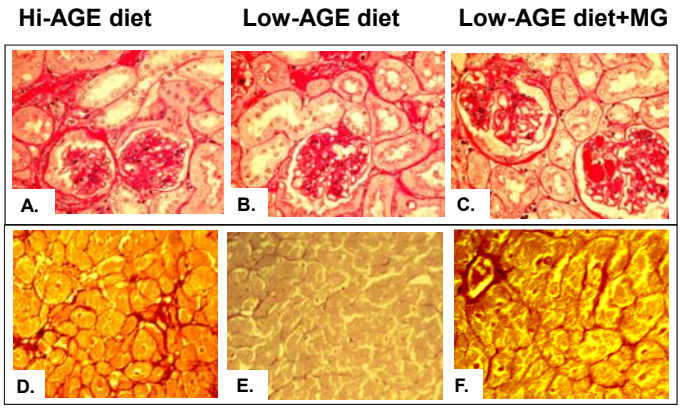
Normally, B6 mice are resistant to CVD/CKD, so AGEs trump genetics.

What is in the diet, is it AGEs, or calories in the diet?

Calorie-Restriction Increases Lifespan and Decreases CVD

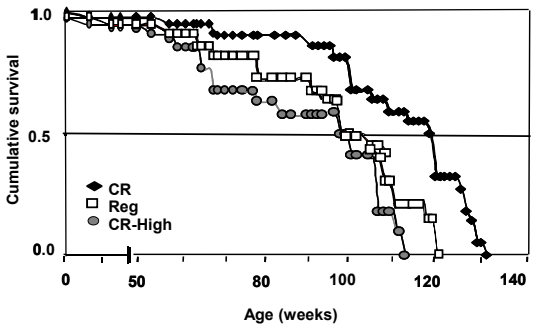
Since Calorie-Restriction Decreases Intake of AGEs, What is it in the Calorie-Restricted Diet that Reduces CVD and CKD?

We Tested This By Varying The Amount Of Ages In The Diet.



Hi-AGE diet causes CKD/CVD in low risk subjects.

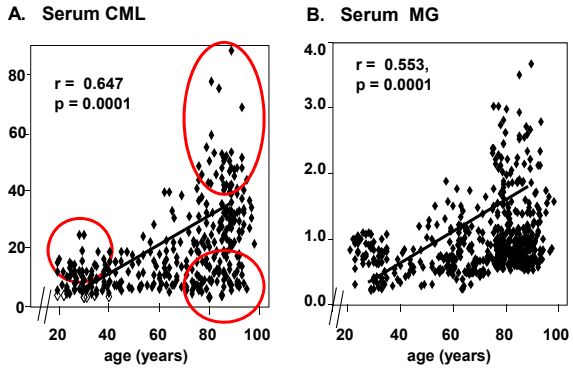
Effect of a Low AGE Diet on Lifespan



The shortened lifespan was due to AGEs in the diet, since the addition of AGEs to a calorie restricted diet also shortened lifespan.

When does this process begin in normal humans?

Studies in Normal Volunteers



The accumulation starts at an early age.
The wide range matches renal function data in BLSA.
Are there significant amounts of AGEs in food?
Which foods contain AGEs, & how can one avoid AGEs?

Oxidant (AGEs) Content of Common Foods Varies Widely, by Cooking Method

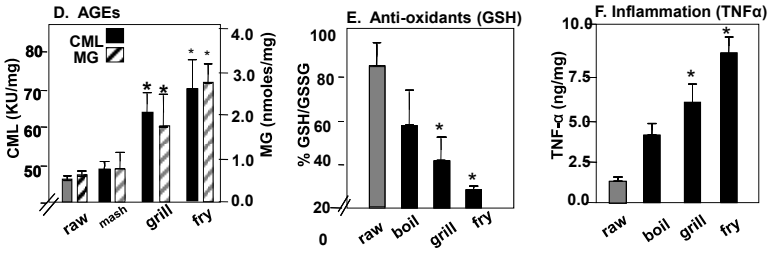
The AGE Content Depends on Temperature of Cooking

	Regular diet (U/mg)		Low AGE diet	
Beef:	broiled	5367	→ STEWED	2000
Chicken:	broiled	5245	→ BOILED	1011
Salmon:	broiled	1348	→ RAW	502
Potato:	fried	1522	→ MASHED	17

The levels of AGEs in foods depend largely on the method of cooking, varying between 2-90 fold between boiling and frying in potatoes, for instance. Data are shown as CML, based on ELISA.

Do the AGEs in these foods have biological activity?

The Method of Preparation Determines the Amount of AGEs In Red Meat Extracts and their Biological Effects

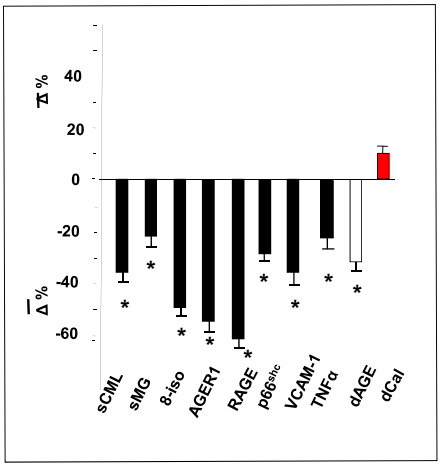


Does a decrease in oxidant intake Reduce OS in normals?

If so, how long does it take to see changes?

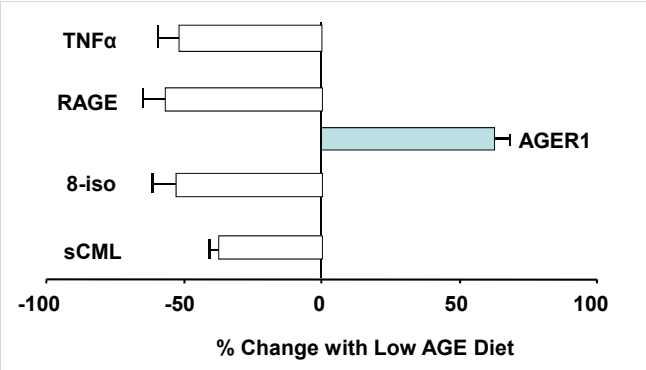
Dietary AGE Intake was Decreased for 6 months In Healthy Adults who Previously Consumed a High AGE Diet

Intervention: simply change cooking methods, no change in nutrition.



Those who love barbecued foods can be rescued!!
Does this apply to CKD, where levels are high at baseline?

Intervention: A Low- AGE diet (30-50% decrease);
CKD 2-4 Patients for a period of 4 weeks



Reduced intake of oxidants (AGEs) very quickly (4 wks) reduces OS in CKD Patients and restores AGER1. Thus, it appears to be effective in aging adults and CKD patients.

Mechanisms??

Reduced Exogenous AGEs

↑ **AGER1** ↓ **sAGEs, Oxidant Stress**

Preserve Anti-OS Reserves ↓Infl

??Prevention of ↓RF in Aging

Summary and Conclusions

- Does everyone get ↓RF as they age? Not all
- Are AGEs and OS involved? Yes
- Do ↑↑ oxidants/AGEs induce ↓ RF in aging? Yes
- What are the sources of oxidants? Exogenous
- What are the mechanisms? ROS formation
- How might one prevent or treat ↓ RF in normal adults, prevent or treat the CKD of aging?
  Reduce AGE formation or intake
- Why does it matter, i.e. why bother to treat?

The kidney defends against high levels of OS.

Thus, ↓RF leads to ↓anti-Oxidant reserves, ↑OS and ↑risk of CVD, AD, and other aging-related diseases.

Co-Workers (MSSM)

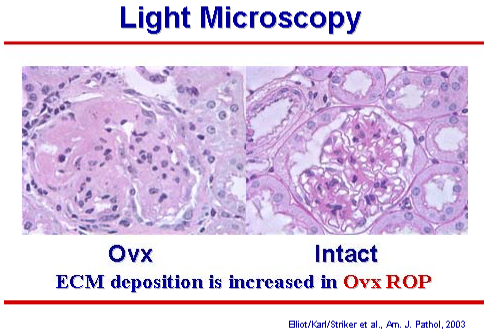
Helen Vlassara

Jaime Uribarri, Cijiang He, James Post, Feng Zheng, Weijing Cai
Vittoria Esposito, Fabrizio Grosjean

Collaborators

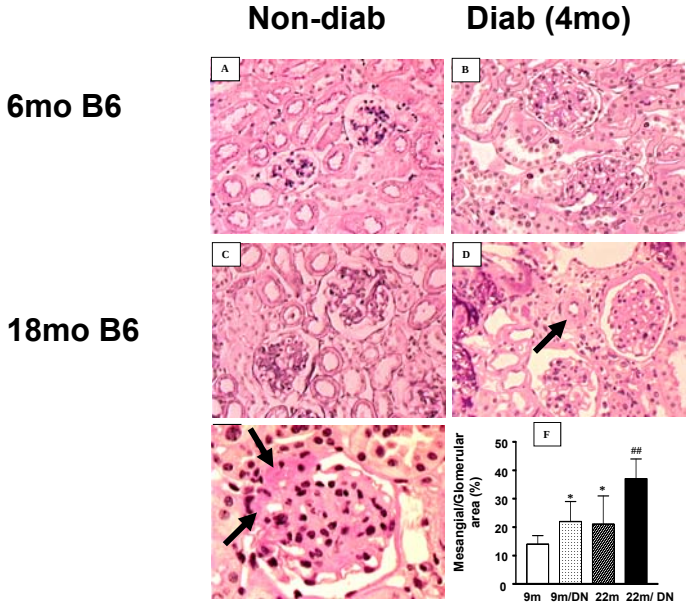
Edward Fisher	Mount Sinai School of Medicine	New York
Theodore Koschinsky	Diabetes Research Institute	Dusseldorf, GE
Masakazu Hattori	Joslin Diabetes Center	Boston, MA
Michael Steffes	University of Minnesota	Minneapolis, MN
Scott Grundy	University of Texas	Dallas, TX
Gloria Vega	University of Texas	Dallas, TX
Alan Stitt	Queen's University	Belfast, UK
Andrzej Krolewski	Joslin Diabetes Center	Boston, MA
Giuseppe Pugliese	La Sapienza University	Rome, Italy
Umberto Di Mario	La Sapienza University	Rome Italy
François Cambien	INSERM	Paris, France
Many others ----		

Estrogen is an anti-oxidant/infl agent!



This may explain the increase in CKD/CVD seen in post-menopausal.

↑Infl/OS in Aging promotes DN in Resistant Strains



↑Infl/OS in Aging promotes DN in Resistant Strains