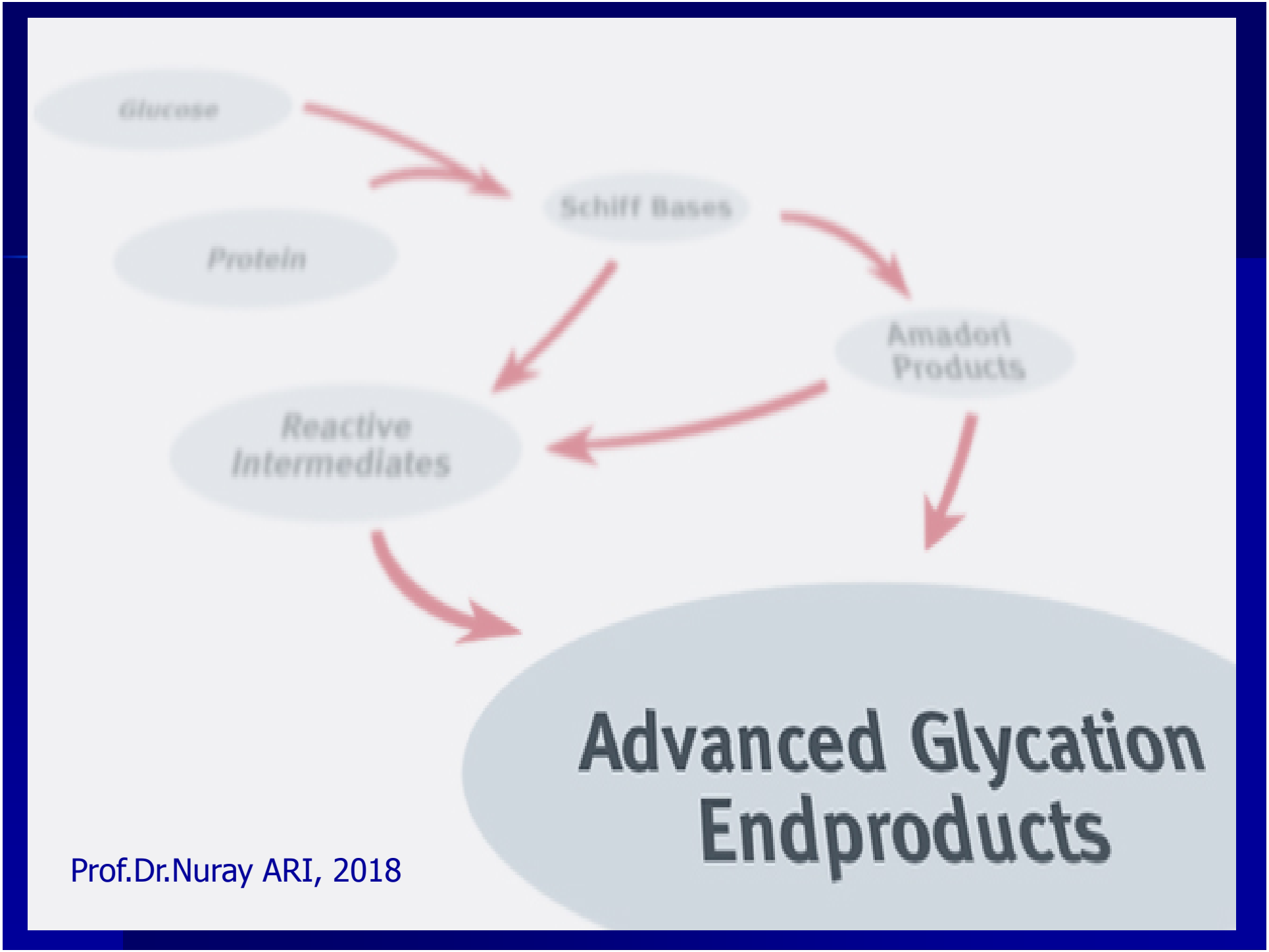
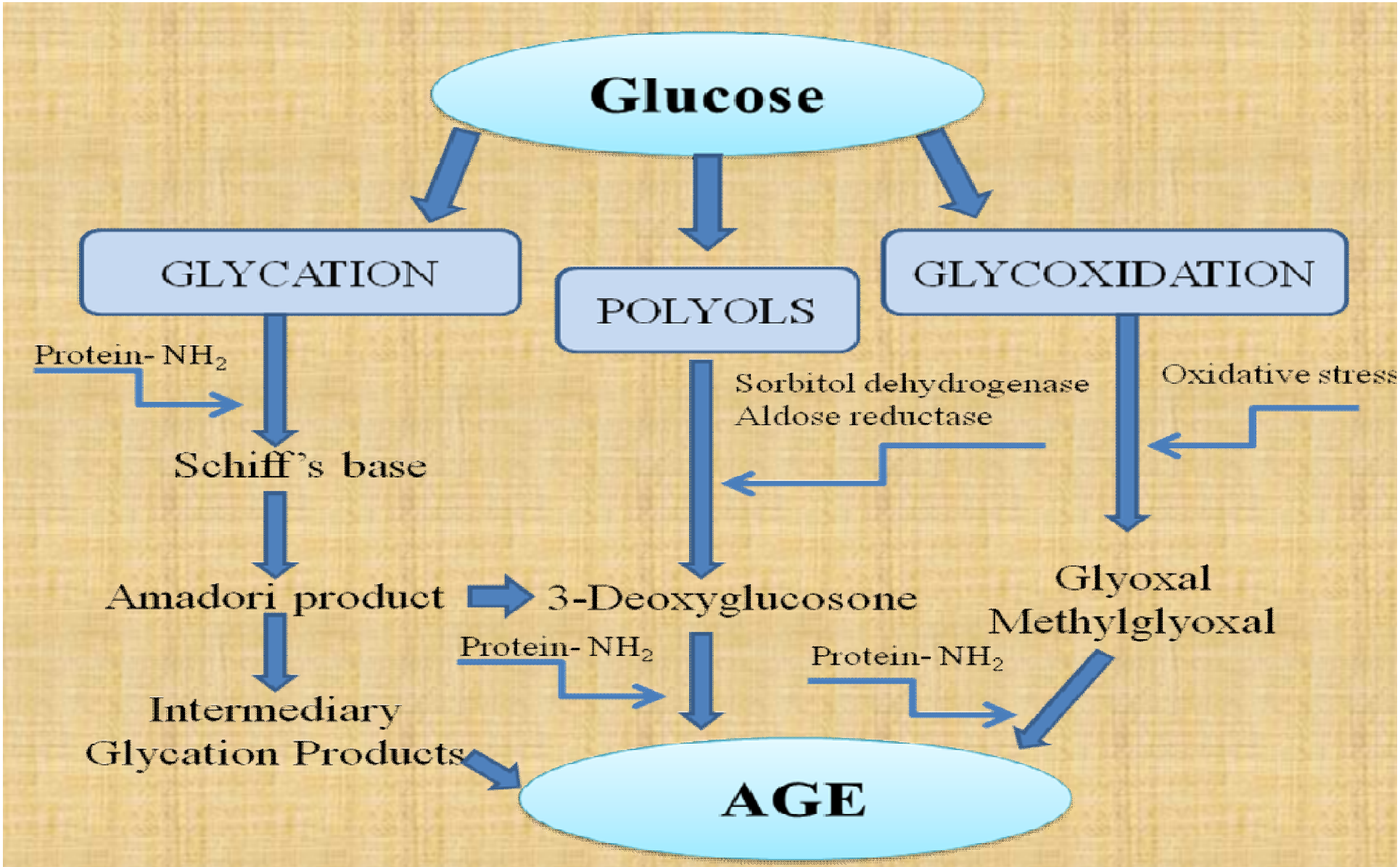


Prof.Dr.Nuray ARI, 2018

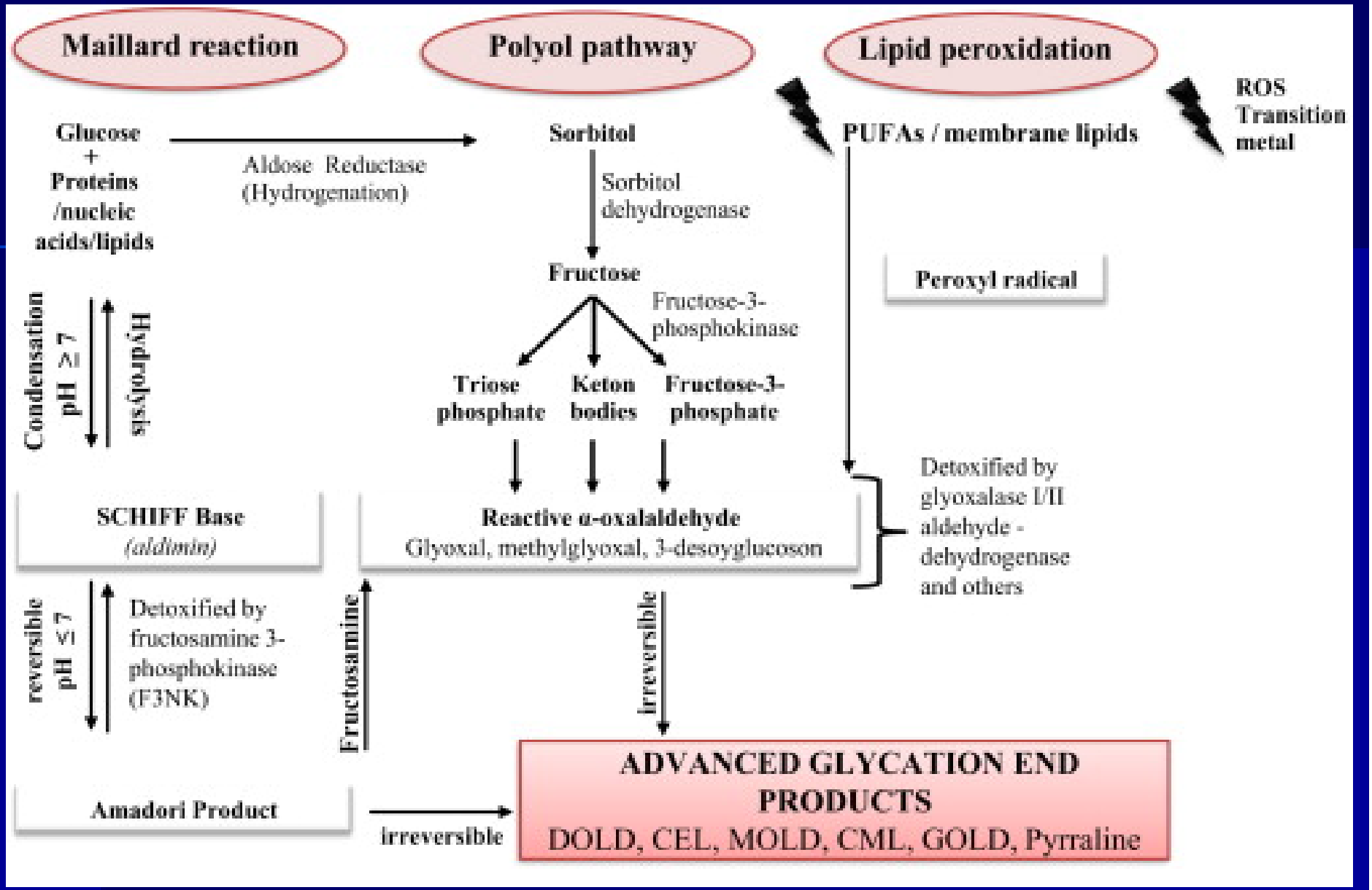
Why should we worry about them?

- inflammation
- atherosclerosis
- kidney damage
- neurodegenerative disease
- muscle loss
- cancer cell metastasis
- insulin resistance
- alterations in cell receptors
- a shorter life
- Oxidation



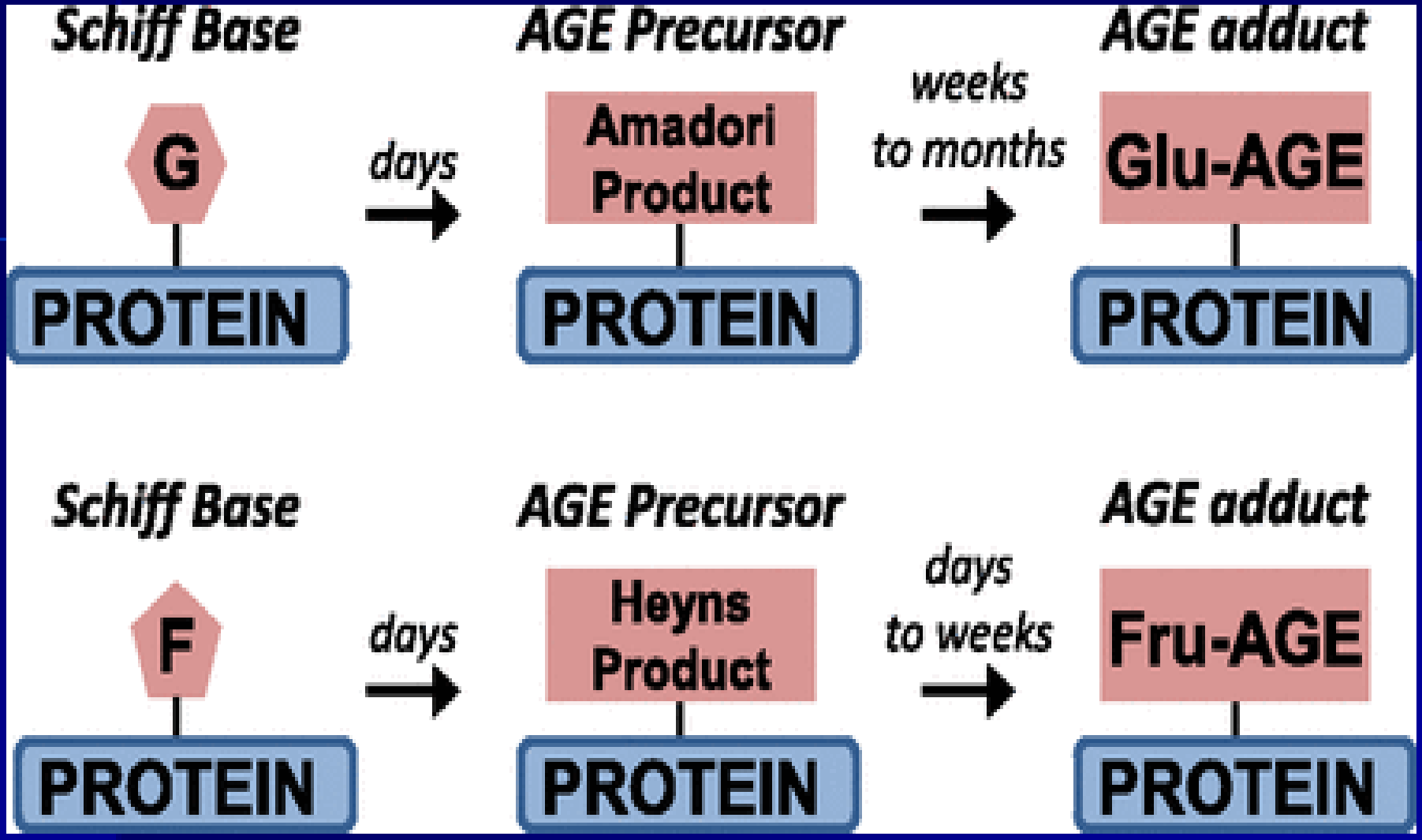
Formation of AGEs by three different mechanisms

Int J Pharm Pharm Sci, Vol 6, Issue 9, 42 47. Dhodi et al.



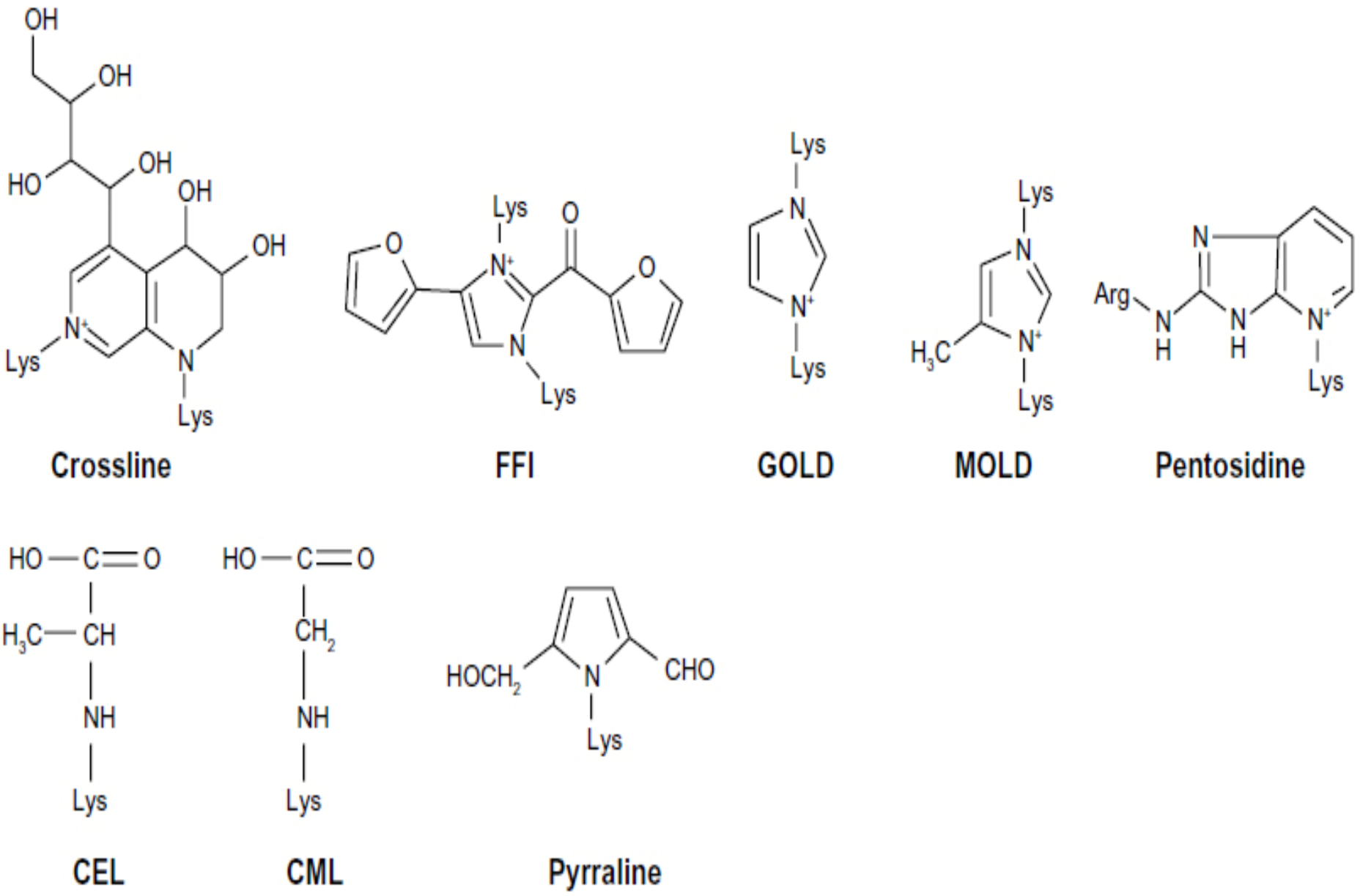
Formation of advanced glycation end products *in vivo*

Redox Biology 2:411-429, 2014. Ott C et al.



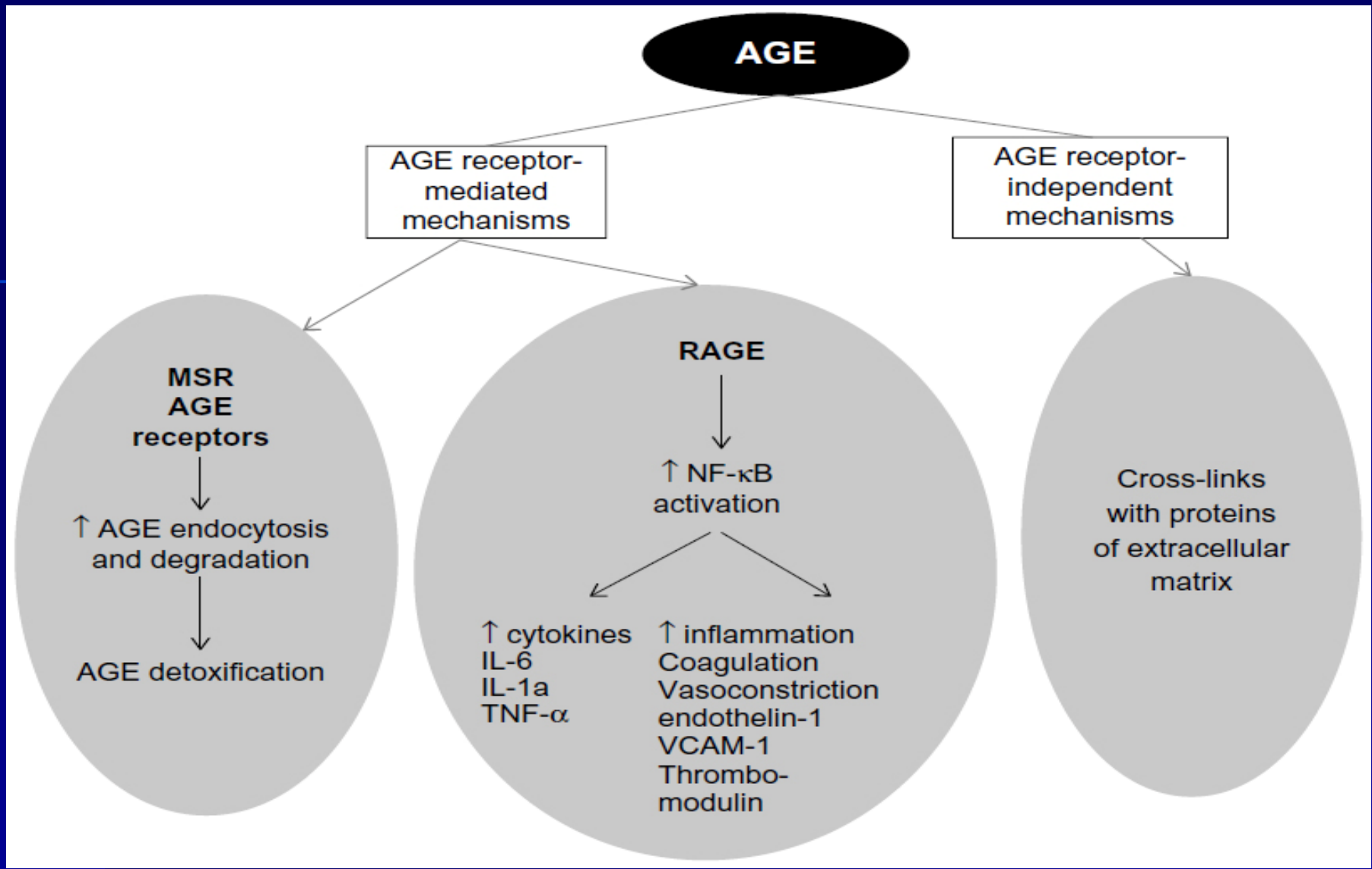
Fructose- and glucose-derived AGE formation.

Diabetes. 2016, 65(12):3521-3528. ***Diabetic Cardiomyopathy: The Case for a Role of Fructose in Disease Etiology.*** Delbridge LM . et al.



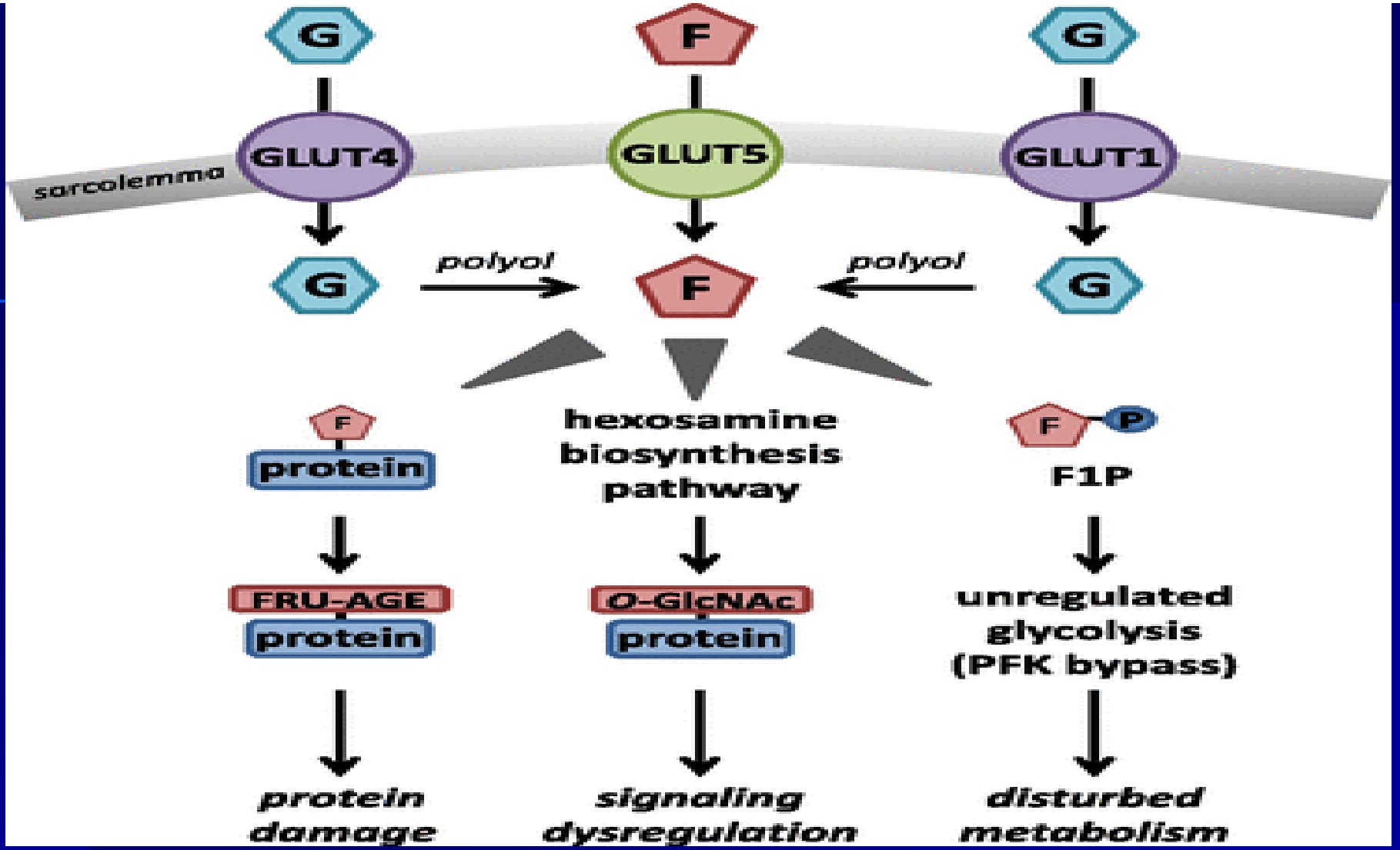
Chemicall structure of some advanced glycation end products (AGEs).

Diabetes, Metabolic Syndrom eand Obesity: Targets and Therapy (Dove Press). Palimeri et al, 8 : 415—426, 2015



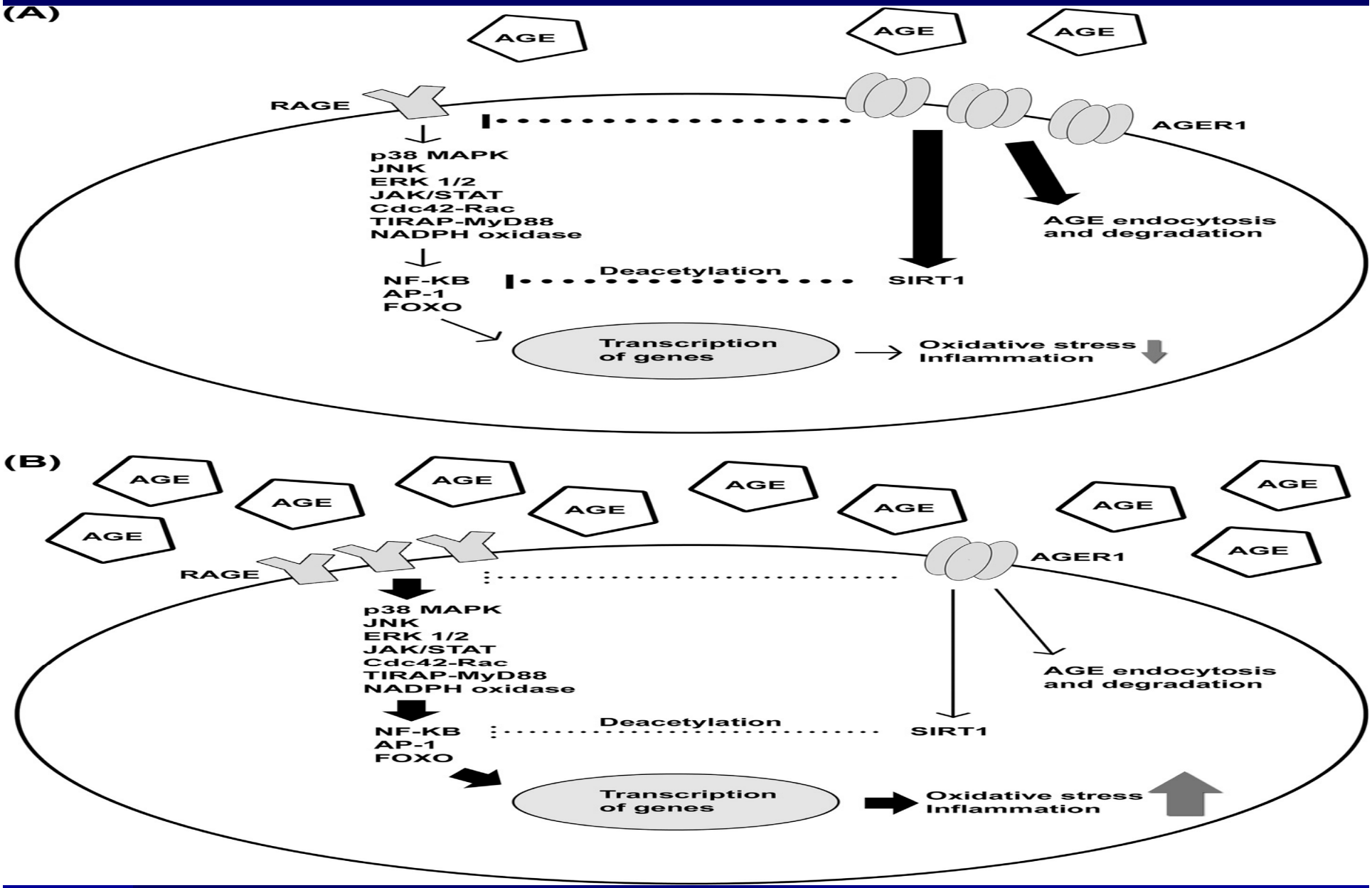
Schematic representation of advanced glycation end product (AGE) mechanisms of action.

Diabetes, Metabolic Syndrom eand Obesity: Targets and Therapy (Dove Press). Palimeri et al, 8 : 415—426, 2015



Potential pathways of direct fructose-induced cardiomyocyte actions. Fructose can enter cardiomyocytes via the GLUT5 fructose-specific transporter and be produced from glucose via the polyol pathway to participate in AGE protein damage, *O*-GlcNAcylation of signaling proteins, and glycolytic disturbance.

Diabetes. 2016, 65(12):3521-3528. Delbridge L.M et al.



AGE interaction with RAGE and AGER1 in conditions with different AGE burdens. A: In conditions with a low AGE burden B: In conditions with a prolonged high AGE burden

M.W. Poulsen et al. / Food and Chemical Toxicology 60 (2013) 10–37

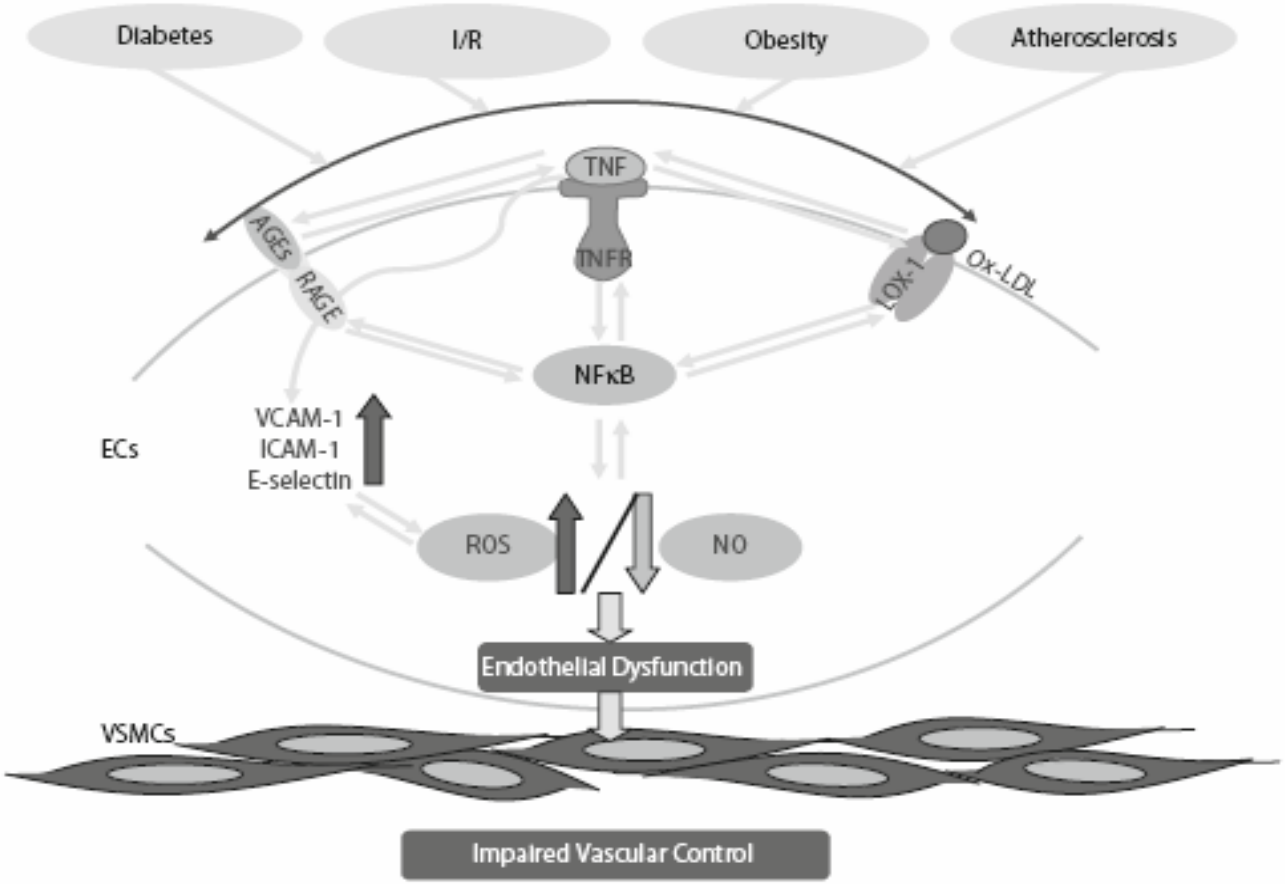
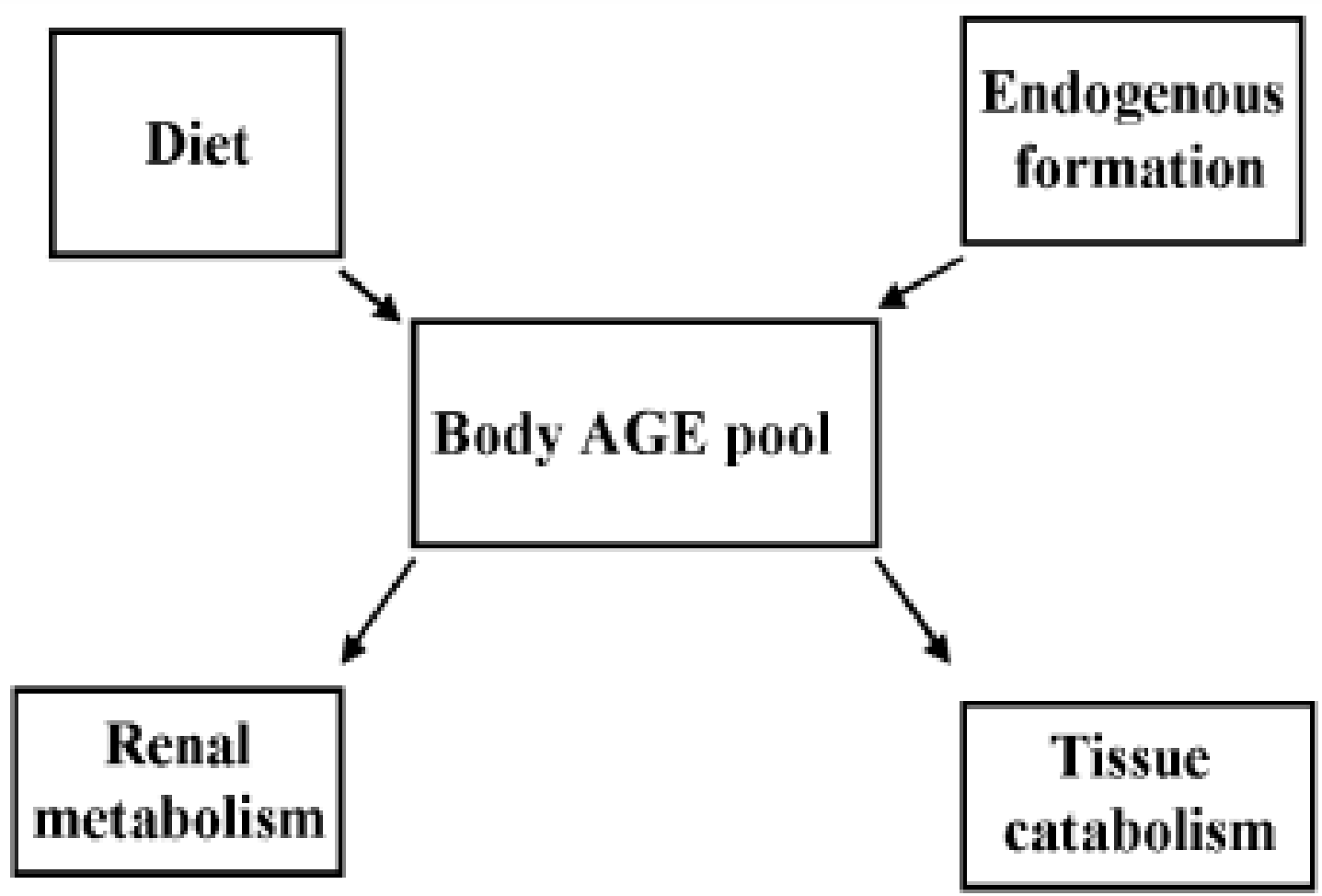


Fig. 1 The indicators of endothelial dysfunction in cardiovascular diseases (CVD) are portrayed. Normally, endothelial cells regulate the homeostasis of the vessel wall. The healthy endothelium is not leaky, anti-adhesive and is able to relax vascular smooth muscle cells. However, when risk factors (diabetes, ischemia/reperfusion, obesity and atherosclerosis etc.) disturb endothelial cells, which induce endothelial dysfunction and vascular remodelling. We have an impaired vascular control when the damaged endothelium is leaky, sticky and unable to relax vascular smooth muscle cells. In brief, central to the endothelial dysfunction is oxidative stress. The oxidative stress is induced by the production of reactive oxidative species (ROS) and this induces NF-κB. Key to the production of ROS is AGE/RAGE and TNF-α signaling, but ox-LDL/LOX-1 signaling is also involved in ROS production. The interactions among oxidative stress, AGE/RAGE, TNF-α/TNFR and ox-LDL/LOX-1 are because oxidative stress induces NF-κB, and this transcription factor can induce AGE, TNF-α and ox-LDL expression; and TNF-α can induce RAGE and LOX-1 expression. Thus, the oxidative stress of diabetes, begets more oxidative stress, eventually inducing endothelial dysfunction, because of decreased bioavailability of nitric oxide (NO, due to the reaction between NO and $O_2^{\cdot -}$)

Mechanism of action	Therapeutic agent	Biological effects
Dietary restriction of AGE		Animal studies[31,50,75–77] Prevents/Improves Insulin resistance Abdominal obesity/body weight Diabetes mellitus type 2 Diabetic nephropathy Diabetic-impaired wound healing Extends life span Human studies Healthy subjects[78–80] ↓ Basal oxidative stress ↓ Inflammation ↓ Serum AGEs Improves markers of insulin resistance Subjects with diabetes or renal failure[13,15,34] ↓ Serum AGEs ↓ Inflammation Improves vascular function and insulin resistance
Blockage of AGE formation	Aminoguanidine[83–85]	Animal studies ↓ Retinopathy ↓ Nephropathy ↓ Neuropathy
	N-(2-Acetamido Methyl) hydrazinecarboximide amide hydrochloride (ALT-946)[86,87]	↓ Nephropathy
	3-benzyloxycarbonylmethyl-4-methyl-thiazol-3-ium bromide (C36)[88]	↓ Diabetic cardiovascular dysfunction
	Pyridoxamine[90,91]	↓ Nephropathy ↓ Dyslipidemia
Cross-link breakers	N-phenacylthiazolium (PTB)[92]	Animal studies ↓ AGE
	Alagebrium (ALT-711)[93,94,96]	Animal studies ↓ Diabetic cardiomyopathy and atherosclerosis ↓ Nephropathy Human studies ↓ Diastolic heart function
RAGE blockade	sRAGE[100–103]	Animal studies ↓ Diabetic atherosclerosis and retinopathy (sRAGE)
	Antihypertensive drugs[99]	Antioxidative properties – prevention of diabetic vascular complications?
	PEDF[99]	Antioxidative properties
	Statins[99]	Antioxidative properties
	Bisphosphonates[99]	Antioxidative properties
	PARP inhibitors[104,105]	Animal studies ↓ Early peripheral diabetic neuropathy Improve endothelial and myocardial function
Other agents	Kremezin (AST-120)[106]	↓ AGE levels in chronic renal failure

Interventions targeting the advanced glycation end product (AGE) pathway

Diabetes, Metabolic Syndrom eand Obesity: Targets and Therapy (Dove Press). Palimeri et al, 8 : 415—426, 2015



A. XANTHIS et al ., 72, (8), 2007, J FOOD SCIENCE

- 10% of dietary AGEs are absorbed.
- Of this 10%, about 1/3 are excreted in the urine within 3 days.

Food item	AGE content[b]
Salmon, raw (90 g)	502
Salmon, broiled (10 minutes, 90 g)	1,348
Beef, boiled (1 hour, 90 g)	2,000
Beef, broiled (15 minutes, 90 g)	5,367
Beef, stir fried (20 minutes) and broiled (15 minutes, 90 g)	6,166
Chicken, boiled (1 hour, 90 g)	1,011
Chicken, broiled (15 minutes, 90 g)	5,245
Beans, red kidney, raw (100 g)	116
Beans, red kidney, canned (100 g)	191
White potato, boiled (25 minutes, 100 g)	17
French fries (100 g)	1,522
Broccoli (100 g)	226
Tomato (100 g)	23
Apple (100 g)	13

AGE content in commonly consumed foods

Notes: AGE content denotes kilounits per serving; AGE measured by enzyme-linked immunosorbent assay using an antibody against N-carboxymethyl lysine.

Diabetes, Metabolic Syndrom eand Obesity: Targets and Therapy (Dove Press). Palimeri et al, 8 : 415—426, 2015