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Review

Aging and glycoxidant stress

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ABSTRACT

Aging and related diseases are accompanied by increased Oxidative Stress (OS) and accumulation of Advanced Glycation End products (AGEs). One important component of AGEs accumulation with aging appears to be the sustained exposure to dietary AGE (dAGEs), which contributes to overloading of anti-AGE receptors and depletion of anti-oxidant reserves. In this review, we present experimental animal and human data which support this postulation. Lowering the content of AGEs in the normal diet significantly prevents AGEs accumulation and the increased OS caused by aging and also extends lifespan in mice. In humans, short-term trials indicate that a Low AGEs diet reduces oxidant burden and inflammatory markers. Long-term studies are in progress and will help establish definitive causality between age-related disease states and modern dietary practices in Western societies.

Key words: Advanced Glycation End products, AGEs, AGE receptors, Aging, Glycoxidant stress, Inflammation, Oxidative stress

INTRODUCTION

Aging and related chronic diseases are accompanied by increased Oxidative Stress (OS), which can directly affect the function of different tissues and organs.[1,2] Since Advanced Glycation End products (AGEs) and OS are two mutually enhancing and tightly linked processes, it is likely that the accumulation of AGEs observed in the aging population is an important factor in the pathogenesis of the increased OS.

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Steady-state serum AGEs levels reflect the balance of endogenous formation, exogenous supply (AGEs consumed with the standard diet or inhaled via tobacco smoking), tissue degradation and their renal excretion.[3-6] Therefore, elevated circulating AGEs levels in aging could result from increased endogenous formation, increased exogenous supply, decreased tissue degradation, decreased renal excretion or a combination of these factors.

ENDOGENOUS FORMATION OF AGEs

AGEs are a group of heterogeneous compounds that form constantly in the body under physiologic conditions, although their rate of formation is markedly increased in the presence of hyperglycemia and increased OS.[3-10] AGEs form via non-enzymatic reac-

tion between reducing sugars, such as glucose, and free amino groups residing on proteins, lipids and nucleic acids. These reactions form a series of intermediates that are initially reversible, but ultimately generate a series of more stable products known as AGEs. AGEs may also form by auto-oxidation of glucose or through the glycolytic pathway, but also from non-glucose sources including lipid and amino acid oxidation.[3-6,8,10] In addition, neutrophils, monocytes and macrophages, upon inflammatory stimulation, produce myeloperoxidase and activate Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase, which can lead to new AGEs by way of amino acid oxidation.[3-6,11,12]

Binding and activation of cellular AGE Receptor (RAGE) by AGEs or any other ligand can also promote OS and AGE formation via the NADPH oxidase and the myeloperoxidase pathways.[3-6,11,12] Another potential mechanism of AGE formation is the polyol pathway. Glucose entering the polyol pathway may form AGEs via reactive intermediates, i.e. glyoxal, methylglyoxal or 3-deoxyglucosone, as well as via depletion of NADPH or glutathione raising intracellular OS, all of which indirectly result in increased formation of AGEs.[3-6,13,14]

Several immunoassay-based tests have established higher levels of common AGEs, such as ε-N-carboxymethyl-lysine (CML) or methylglyoxal (MG) in older persons who are otherwise healthy[15] (Figure 1). The frequent finding in the aged population of increased OS,[1,2] a state known to promote AGEs formation, supports the notion of increased endogenous AGEs formation in the elderly.

EXOGENOUS AGEs

The reactions of reducing sugars with amino acids as well as the generation of reactive aldehydes from either glucose or lipid oxidation also take place in food and these reactions are markedly accelerated by high temperature.[3-6,16-20] Therefore, the content of AGEs in the diet depends on its protein, lipid and carbohydrate content as well as on the method of cooking used, especially the temperature of preparation. Foods cooked at high temperature for long periods of time in dry conditions have the highest AGE content, especially those with a high fat content[16] (Table 1).

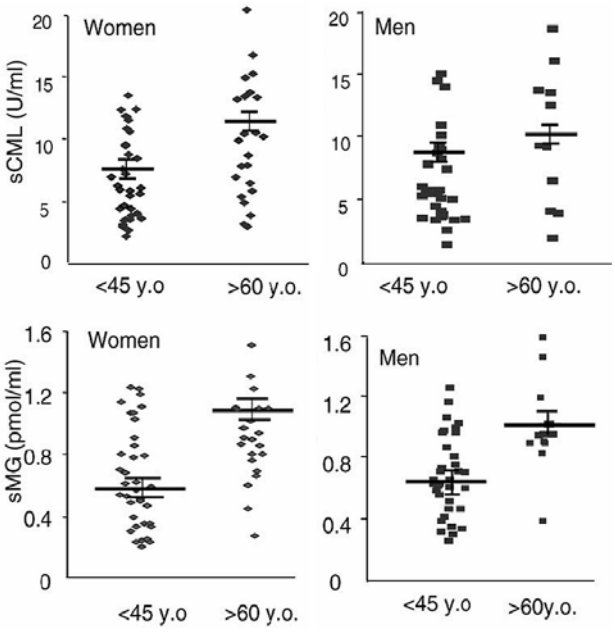

Figure 1. Levels of serum AGEs, ε-N-carboxymethyl-lysine (sCML) and methylglyoxal (sMG) derivatives are elevated in older men and women. Fasting blood was obtained in older (60-80yrs old) and younger (18-45yrs old) healthy participants for measurement of CML and MG derivatives by ELISA. Data are presented as mean±SEM (*$p<0.05$).[49]

A portion of the ingested AGEs and/or various forms of glycation intermediates derived from the food are absorbed and enter the circulation where they may react with cellular and extracellular components, thus increasing the AGE pool. Food-derived AGEs induce protein cross-linking and intracellular OS similar to their endogenous counterparts when tested in vitro using human endothelial cells.[21] The same pro-oxidant and pro-inflammatory properties are also associated with exogenous AGEs and these can be transferred onto native proteins or lipids. For example, LDL samples from diabetic subjects exposed to a High-AGE diet for several weeks became AGE-modified and promoted MAPK phosphorylation, NF-κB activity and VCAM-1 secretion by cultured human endothelial cells, compared to the relatively inactive LDL extracted from diabetic subjects of similar glycemic control but exposed to a Low-AGE diet.[22]

Several studies in different animal models have now established that dietary AGEs could play a sig-

Table 1. Thermal Exposure Determines AGEs Content of Common Foods

Foods	AGE* (U/g)	Serving** (g)	AGE/Serving (kU/ or Ux10^3)
Frankfurter, boiled x 7 min	74850	90	6736
Frankfurter, broiled x 5 min	112697	90	10143
Pork chop, pan fried x 7 min	47526	90	4277
Beef and pork links, pan fried	54255	45	2441
Chicken breast, skinless cubes, pan fried x 15 min	61221	90	5510
Chicken breast, skinless cubes, steam x 10 min and broiled x 12 min	56348	90	5071
Chicken breast, skinless cubes, pan fried x 10 min and boiled x 12 min	63398	90	5706
Chicken breast, skinless cutlet, raw	7686	90	692
Chicken breast, skinless cutlet, boiled x 1 hr	11236	90	1011
Chicken breast, skinless cutlet, broiled x 15 min	58281	90	5245
Chicken breast, skinless cutlet, fried x 8 min	73896	90	6651
Chicken breast, skinless cutlet, microwave x 5 min	15245	90	1372
Chicken breast, skinless cutlet:-Roasted, barbecue sauce	47673	90	4291
Chicken breast, skinless cutlet:-Roasted, breaded	45580	90	4102
Chicken breast, skinless cutlet:-Roasted, breaded, microwave, 1 min	57299	90	5157
Salmon, breaded, broiled x 10 min	14973	90	1348
Salmon, raw	5573	90	502
Salmon, smoked	5718	90	515
Trout, raw	7830	90	705
Trout, roasted x 25 min	21383	90	1924
Tuna, broiled with soy x 10 min	51133	90	4602
Tuna, broiled with vinegar dressing x 10 min	51497	90	4635
Tuna loaf, roasted x 40 min	5895	90	531
Tuna, roasted x 25 min	9189	90	827
Tuna, white, canned in oil, Albacore	17396	90	1566
Whiting, breaded, oven fried, 25 min	87743	90	7897
Egg yolk, boiled x 10 min	12134	15	182
Egg yolk, boiled x 12 min	18616	15	279
Egg white, boiled x 10 min	442	30	13
Egg white, boiled x 12 min	573	30	17
Egg white powder, cooked with margarine	10440	10	104
Egg, fried with margarine	27494	45	1237
Almonds, roasted	66514	30	1995
Mayonnaise	94010	5	470
Mayonnaise, low fat[1]	22011	5	110
Walnuts, roasted	78874	30	2366

*AGE denotes $^{\varepsilon}$N-carboxymethyl-lysine (CML),[16] determined by ELISA (4G9).
**Serving: shown in common household measures or portions expressed in grams (g) for solids and in milliliters (ml) for liquids.

nificant role in promoting type 1 diabetes mellitus in non-obese diabetic (NOD) mice,[23] insulin resistance and type 2 diabetes in *db/db (+/+)* or fat-diet fed mice,[24,25] atherosclerosis in apoE deficient mice,[26,27] diabetic nephropathy,[28] impaired wound healing in *db/db (+/+)* mice[29] and, importantly, decreased lifespan of normally aging C57BL6 mice.[30] A short period of exposure to a Low-AGE diet of diabetic patients, as well as of non-diabetic peritoneal dialysis patients, resulted in a significant decrease in the levels of AGEs and of inflammatory mediators.[31-33] Also supportive were studies on the acute effects of dietary AGEs in

vivo: a single High-AGE meal administered to diabetic patients caused marked but reversible impairment of flow-mediated vasodilatation, as compared with an isocaloric Low-AGE meal.[34] The flow-mediated impairment induced by the High-AGE meal was prevented by pre-treatment of the subjects with high doses of oral benfotiamine, further supporting the pro-oxidant basis of these events.[35]

We recently studied the impact of short-term modifications of dietary AGEs on circulating and urinary AGEs in a group of five healthy subjects over a period of 9 days.[36] These subjects were placed sequentially, first on a regular meal schedule (~16 AGE Eq/day x 3 days), then on a Low-AGE but isocaloric diet meal schedule (~4 AGE Eq/day x 3 days) and then returned to the regular diet (x 3 days). The reduction of dietary AGEs intake was associated with an average decrease of serum AGE levels by 30%. Significant shifts were also noted in urinary AGE excretion in response to altered dietary AGE intake, corresponding to the circulating AGEs levels.

The above findings strongly support the role of dietary AGEs as significant contributors to the body AGE pool as well as to the increased inflammation and OS in states such as diabetes or aging. We have now estimated the dietary AGEs intake in healthy subjects and found no evidence of increasing dietary AGE intake with aging.[37] However, sustained high dietary AGE intake in the presence of declining renal function, as seen in the aging population, could easily increase circulating and tissue AGE levels.

TISSUE DEGRADATION OF AGEs

Several mechanisms are in place to ensure that excessive AGEs, like other oxidants, are neutralized or removed.[3-6] The AGE detoxification system includes enzymatic mechanisms such as the glyoxalase-I and II system, anti-oxidant defenses, circulating proteins that trap AGEs, receptor-dependent intracellular uptake and destruction as well as urinary excretion. Thus, methylglyoxal, a highly reactive AGE precursor molecule, is detoxified by glyoxalase I and II at a rate proportional to the cytosolic levels of GSH.[3-6,15,16] Another route is through its reduction, catalyzed by aldehyde reductase (AKR1), aldose reductase (AKR2) and carbonyl reductase (CR).[3-6,14,38] Also, a group of circulating proteins such as lysozyme, defensins and lactoferrin bind AGEs, preventing them from causing cellular toxicity or from binding to other molecules.[39-41]

There are two types of cell surface AGE receptors, those that bind AGEs and initiate cell activation and those that bind and degrade AGEs. RAGE is the best studied receptor of the first category; it recognizes AGEs as one of many ligands and initiates OS. The second group of receptors includes AGER1, AGER3 and CD36.[3-6] The best evaluated in this category of AGE-receptors is AGER1, which has been found to have marked anti-oxidant properties.[3-6,42-44]

AGER1 AS A MULTIFACTORIAL ANTI-OS RECEPTOR

AGER1, a ~50 kD protein present on cell surface, endoplasmic reticulum and possibly on mitochondrial structures (unpublished data), is the most extensively studied receptor involved in ligand endocytosis and processing.[3-6] In addition to contributing to AGE removal, AGER1 opposes AGE-mediated RAGE, MAPK and Nf-kB-dependent inflammatory responses. This appears to involve inhibition of AGE-mediated activation of EGFR and the EGFR-dependent tyr-phosphorylation.[42] It has also been shown that AGEs promote, and AGER1 suppresses a key OS- and lifespan-regulatory adaptor, protein $p66^{Shc}$ serine phosphorylation, that is shown to cause FKHRL1 inactivation, prolonged suppression of MnSOD and thus oxidant injury.[43] These findings establish the fact that AGER1 regulates intracellular OS and normally protects against oxidant injury. However, the function of AGER1, the chief endocytic AGE receptor, might be suppressed in aging as it is in chronic high OS states such as diabetes.[44]

A recent study in mice provided significant insights into AGER1 activity and age. Young mice were randomized to either a Low- (Low-AGE) or a Regular (Reg-AGE) diet for about 3 years. When examined in old age, the mice exposed to the Low-AGE diet had reduced levels of AGEs, and of OS, less severe age-related insulin resistance, heart and kidney changes and a longer lifespan relative to mice exposed to an isocaloric diet of standard AGE content (Reg-AGE), suggesting that reduced amounts

of certain glycoxidants in the standard diet may delay the aging process by lowering the net OS baseline[30] (Figure 2, 3). In addition, the expression and function of AGER1, the receptor that abrogates the effects of AGEs, was enhanced, and RAGE, which promotes OS, was suppressed in the Low-AGE mice, thus presenting a higher AGER1-to-RAGE ratio than that found in the Reg-AGE mice (Figure 4). The increased expression of AGER1 in the Low-AGE mice suggests that AGER1 can respond to and effectively handle fluctuations in AGE load *in vivo* if the net OS baseline does not exceed a certain threshold. However, under conditions of chronically excessive exogenous AGEs (or a high net OS baseline), AGER1 levels, as observed with other anti-oxidant defenses and scavenger receptors, decrease, indicating that the capacity of the body to handle oxidants is exceeded. This seems to be the case in two chronic conditions associated with high levels of AGEs, diabetes mellitus and renal failure.[3-6] As people grow older, reduced AGER1 activity together with impaired renal function contribute to increasing AGEs levels and hence to increased OS, thereby accelerating tissue injury.

Taken together, these data support the view that the inflammatory response seen in aging represents a response to cumulative and sustained pressure from exogenous oxidants and that the modern diet is a significant source of these oxidants in humans. AGER1 is a multifunctional molecule important for the regulation of OS, and its actions involve new signaling pathways that were not previously linked to AGE-induced cellular or tissue injury or to aging. The sustained nature of elevated OS induced by AGEs may constitute a basis for the progressive depletion of innate defenses later in life, and this may include, or be due to, reduced levels of AGER1. The evidence thus far underscores the importance of systematic evaluation of AGER1 and its relationships to exogenous oxidants during aging. Further research may identify a causality with OS and delineate AGER1 as a new therapeutic target.

RENAL AGE ELIMINATION

AGE-peptides filter across the glomerular membrane and undergo variable degrees of reabsorption and further catabolism by the cells of the renal proximal tubules, while the rest is excreted in the urine.[3-6] A precise and quantitative analysis of the contribution of each one of these processes, however, is lacking in humans.

The important role of the kidneys in the metabolism and excretion of AGEs is demonstrated by an inverse correlation between serum AGE levels and

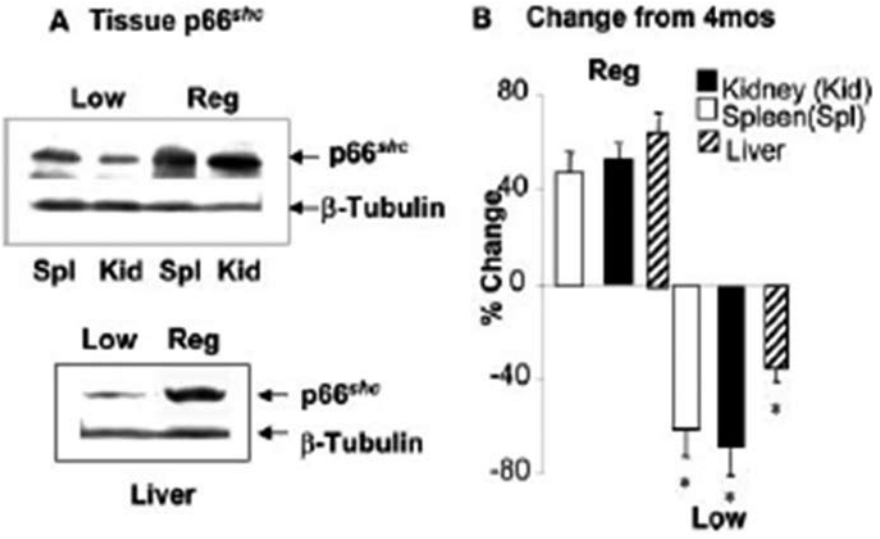

Figure 2. Levels of p66shc protein in kidney, spleen and liver tissues in mice under Low-AGE and Reg-AGE diet. Western blot (A) and densitometry data (B) also indicate the relative change from 4 months of age (baseline). Data shown are mean±SEM of three independent experiments (*$p<0.01$).[30]

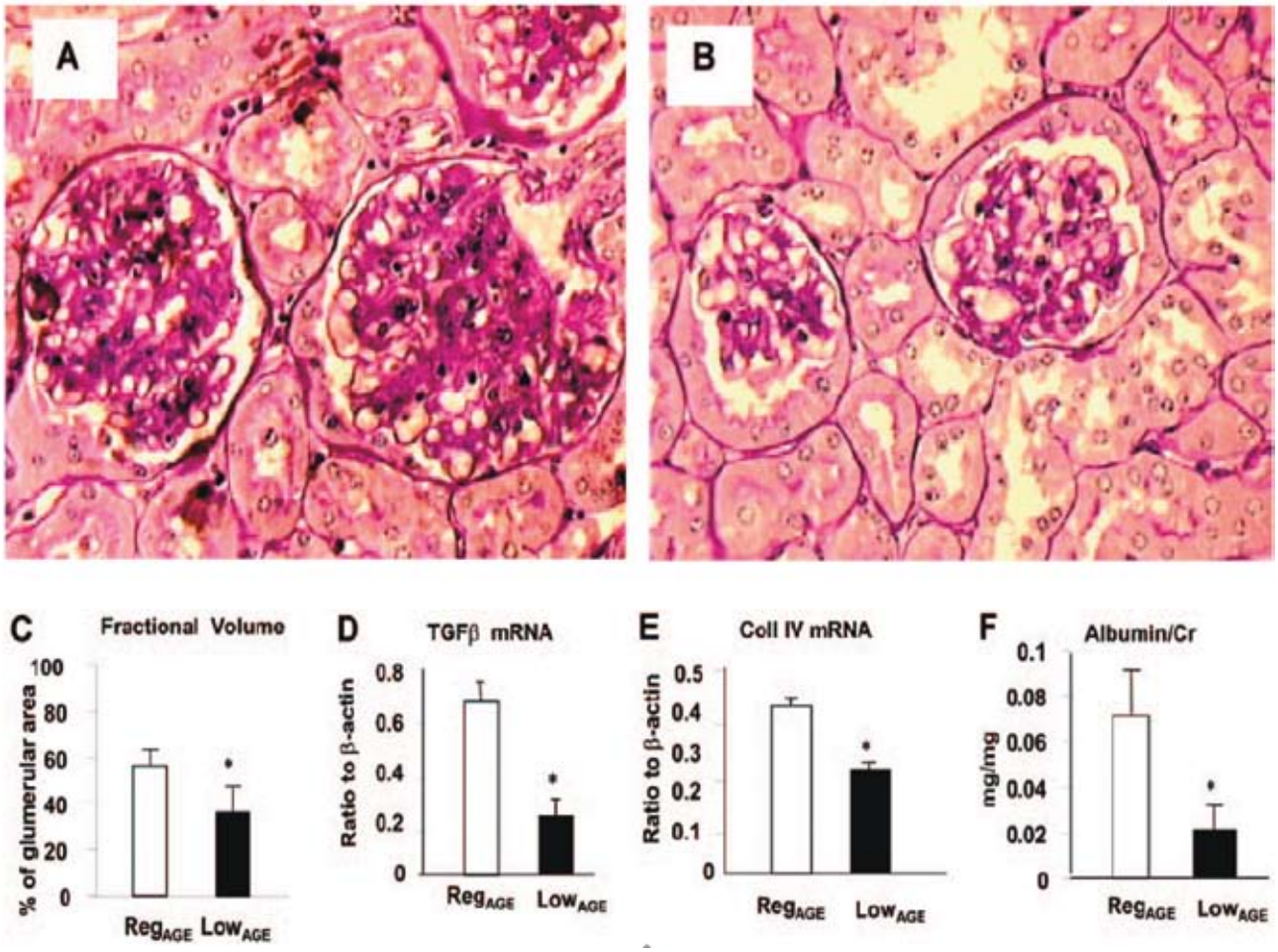

Figure 3. Changes in glomeruli and renal function in mice. **A.** Morphology of renal cortex on Reg-AGE, **B.** Low-AGE, **C.** fractional mesangial volume (*p<0.05), **D.** Transforming Growth Factor-β (TGF-β) (*p<0.05), **E.** collagen type IV (Coll IV) mRNA levels on Reg-AGE versus Low-AGE (*p<0.05) and **F.** Albumin/creatinine ratio (*p<0.05). Data are shown as mean±SEM of triplicate vaues (original magnificationsx20).[30]

renal function (glomerular filtration rate) and by the abnormal handling of an oral AGE load by animals and humans with severe renal disease.[3-6] Therefore, the progressive decline in GFR with aging[45] could explain the high levels of circulating AGEs, an effect that can be magnified by even minimal increases in the rate of endogenous formation of AGEs or else by sustained High-AGE dietary intake. The kidneys are also targets for AGE-induced injury and an alternative or complementary hypothesis would be that the accumulation of AGEs and OS resulting from a lifelong exposure to a High-AGE diet might progressively damage the kidney.

HUMAN AND EXPERIMENTAL DATA ON AGEs AND AGING

Early interference with AGE accumulation by aminoguanidine in rats imparted significant protection against the progressive cardiovascular and renal decline affecting untreated aging animals.[46] We have already mentioned that a long-term High-AGE diet leads to disease and short lifespan in mice, while a long-term Low-AGE diet prevents these effects[3-6,30] (Figure 5).

A pathogenetic role of AGEs in the arterial stiffness and endothelial dysfunction of aging is strongly

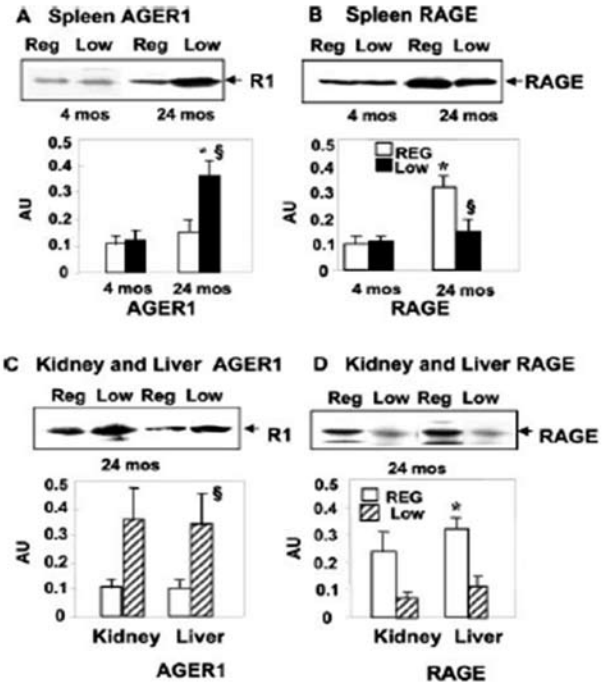

Figure 4. Levels of AGER1 (A) and RAGE (B) protein levels in spleen tissues from Reg-AGE and Low-AGE mice at 4mos (Base line) and at 24mos. AGER1 expression (C) in kidney and liver and RAGE expression (D) in kidney and liver of the same mice groups were also assessed at 24 months by Western Blotting and densitometric analysis (AU). Data are shown as mean±SEM *p<0.01 vs 4month Reg-AGE and § p<0.01 vs 24-month Reg-AGE.[30]

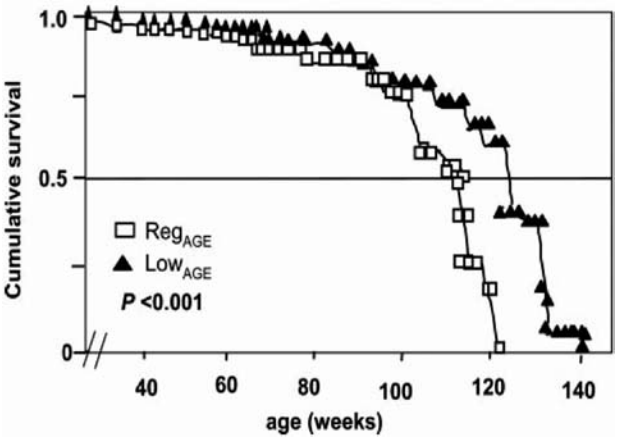

Figure 5. Kaplan-Meier survival curves in Reg-AGE mice (open squares) and Low-AGE mice (filled triangles). Lifespan of the Low-AGE group was significantly longer than the one of the Reg-AGE (p<0.001). Differences between the curves were estimated by the long rank test.[30]

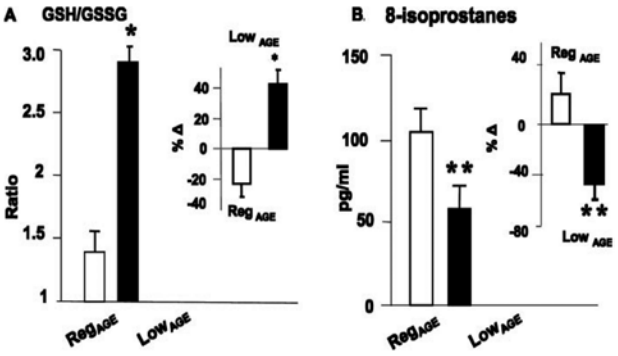

Figure 6. Changes in OS indicators. A:GSH/GSSG ratio. Levels of GSH and GSSG measured in whole blood at 4 (baseline) and 24 months of age. Reg-AGE versus Low-AGE mice *p<0.001). The relative change from baseline is shown in the inset. B: plasma levels of 8- isoprostane are shown as mean±SEM pg/ml. Reg-AGE versus Low-AGE **p<0.01. The relative change from baseline is shown in the inset.[30]

suggested by recent studies in older subjects with known vascular stiffening. The oral administration of alagebrium, a novel non-enzymatic breaker of AGE cross-links, significantly improved arterial compliance and endothelial function and decreased pulse pressure in these subjects compared to placebo.[47,48]

In a recent clinical study that included a large number of healthy elderly subjects, we demonstrated that circulating AGEs increased with age and that dietary AGE intake was an independent correlate of circulating AGEs as well as of hsCRP[37,49] (Figure 1). Furthermore, the circulating AGEs correlate well with the levels of established markers of OS and inflammation[37,49] in mice (Figure 6). These findings support the notion that AGE-activated signal pathways may affect OS levels in healthy adults and that elevated circulating AGEs may be an indicator of underlying anti-oxidant and innate immune defense imbalance.

On the basis of several epidemiological studies,[50] it has been established that a rise in OS among clinically normal individuals may promote insulin resistance and the metabolic syndrome. Consumption of dietary AGEs directly influences systemic levels of AGEs and may result in an early rise in OS and inflammation which, if sustained throughout adulthood, may have significant adverse health consequences for the aging population. This hypothesis should be tested in longitudinal studies as well as in large randomized,

controlled trials to evaluate the effect of dietary AGE restriction on health outcomes.

It must be added that this is not an all-inclusive review since it focuses only on the relationship of ACEs to the aging process. However, there are significant data relating endogenously formed or exogenously provided AGEs with endocrinopathies other than diabetes, such as Polycystic Ovary Syndrome (PCOS), which possibly reflect the aging process of specific organs; these are discussed in detail in reviews or papers dealing with this subject.[51,52]

SUMMARY

AGEs underlie many aspects of the aging process. One of the ways by which AGEs induce changes related to aging is by generating reactive oxidant species, which further promote the formation of AGEs. This sets up a vicious action/reaction cycle, which progressively increases OS and the risk for both micro- and macrovascular disease. Extrapolation of data from animal models suggests that a life-long exposure to the High-AGE content of the standard Western diet leads to prolonged exposure to high levels of exogenous glycoxidants, increased OS and decreased innate immunity, which begin in early adulthood and progress throughout life. These changes could play a key role in the development of the aging process. It is quite possible that a diet with 50% lower AGE content could have substantial beneficial anti-aging effects.

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