Review

Aging and oxidative stress

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Abstract

The scientific establishment has been discussing the relationship between aging and oxidative stress for quite some time now. While we are still far from a general agreement about this subject, there is an impressive amount of data collected that can be used to draw a compelling picture of the events that take place during the human aging process and their correlation with the oxidant status of the organism. In this review, we bring forth the results of some key studies that can help to elucidate the aging-oxidative stress puzzle, as well as to explain which are the fundamental events in this interplay and why their causal relationships remain so elusive. We also put forward here data on the systemic oxidative stress status of a group of 503 healthy human subjects. The data consist of the plasma levels of TBARS and of the nutritional antioxidants, α-tocopherol, β-carotene and ascorbic acid, and of the activity of the antioxidant enzymes, Cu, Zn-superoxide dismutase, catalase and glutathione peroxidase, of red blood cells. The data indicate that a moderate situation of oxidative stress gradually develops during human aging.

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Abbreviations: HPLC, high performance liquid chromatography; LDL, low density lipoprotein; MDA, malondialdehyde; RDA, recommended daily allowance; TBARS, thiobarbituric acid reactive substances

Keywords: Antioxidant enzymes; Human aging; Oxidative stress; α-tocopherol; β-carotene; Ascorbic acid
1. Aging and oxidative stress

The aging process according to Harman (1956, 1972); (Beckman and Ames, 1998) is the accumulation of oxidative damage to cells and tissues, associated with a progressive increase in the chance of morbidity and mortality. During lifetime, an antioxidant network counteracts the deleterious action of free radicals and reactive species on macromolecules. Cells synthesize some of their antioxidants, as the enzymes superoxide dismutase, catalase, and glutathione peroxidase, as well as the peptides with thiol groups, as glutathione, while other antioxidants are obtained from nature through nutrition, as vitamin C, vitamin E, and carotenoids. Long-living animal species have more efficient antioxidant systems and higher liver Cu, Zn-superoxide dismutase activity than shorter-living species (Cutler, 1991). Several repair systems help antioxidant action by the recovery of damaged macromolecules (Cutler and Rodriguez, 2003). Together, these systems play an important role in the ability of the body to respond to the oxidant challenge of using molecular oxygen to drive reactions that yield the necessary energy for life processes.

Oxidative stress is classically defined as a redox unbalance with an excess of oxidants or a defect in antioxidants (Sies, 1985). What are the specific contributions of each component of oxidative stress to human aging? In which degree does a decrease in antioxidants or an increase in oxidants or in the amount of modified macromolecules influence the process of human aging? These issues have not yet been elucidated. There still are many controversies in the literature, the most common being selection of participants to be studied, parameters measured, methods used to achieve the results, and end points selected (Pryor, 2000; Block et al., 2002). It is necessary to consider that diseases that frequently accompany aging have oxidative stress as a major determinant (Ames et al., 1993; Wick et al., 2000). Moreover, the intake of micronutrients important for the antioxidant protection of macro-
molecules has to be evaluated. This last point leads to the current discussion concerning whether the plasma levels show a strict correlation with the intake of antioxidant vitamins (Block, 2001), whether the RDAs are enough to counteract oxidative stress processes (McDermott, 2000), and when pharmacological doses of antioxidants should be recommended (McCall and Frei, 1999; Darley-Usmar and Starke-Reed, 2000).

This article reviews studies dealing with levels of non-enzymatic and enzymatic antioxidants and their relation to parameters of human aging, and provides data on the plasma levels of lipoperoxidation products and of non-enzymatic antioxidants, and on the activity of antioxidant enzymes in red blood cells, in a controlled group of patients.

2. Molecular antioxidants and aging

Most of the published studies concerning aging and oxidative stress have mainly focused on the antioxidant component rather than in oxidized products derived from the action of reactive species on macromolecules. Longevity has been associated with higher \( \alpha \)-tocopherol plasma content in mammalian species, as well as with serum carotenoids, and ascorbic acid (Cutler, 1991). In spite of man showing the highest lifespan among mammals, and so far having the highest levels of antioxidants, most of the studies found an association between aging and decreased levels of molecular antioxidants.

Healthy centenarians studied by Mecocci et al. (2000) showed plasma levels of vitamin E (56 \( \mu \)M) than elderly (42–47 \( \mu \)M) and younger (51 \( \mu \)M) humans, the same pattern being followed by vitamin A. Vitamin C and carotenoids plasma content showed an inverse correlation with increasing age, which was explained by a decreased intake (although non evaluated in the study). The authors concluded that vitamins E and A are of particular importance for longevity.

Similar results were reported by Paolisso et al. (1998) in healthy centenarians from Campanha (southern Italy), that showed higher plasma levels of vitamins C and E than aged subjects (70–99 years), but lower than younger adults (<50 years old). Indeed, centenarians showed a better immunological profile, endocrinological and metabolic characteristics, and nutritional status than aged subjects (Sansoni et al., 1993; Mariotti et al., 1993; Paolisso et al., 1996). It is noteworthy that healthy aging and longevity in the Mediterranean population have been associated with a high nutritional intake of antioxidants (Trichopoulou et al., 1999). Good nutrition in the elderly, both of macro and micronutrients, has been claimed responsible for healthy aging (González-Cross et al., 2001; Barnett, 1994).

Cognitive decline associated with oxidative stress was observed by Berr et al. (2000), that showed an increased risk of cognitive decline during aging associated with low levels of vitamin E, carotenoids and selenium. Similarly, Schmidt et al. (1998), evaluating cross-sectional data from the Austrian Stroke Prevention Study, showed that the decrease in cognition is associated with a decrease in plasma \( \alpha \)-tocopherol, even after adjustment for confounders, including age, sex, years of
education, and smoking. No other measured antioxidant showed any relation with cognition.

Mezzetti et al. (1996) observed that disabled older adults (80–90 years old) have lower plasma vitamin E and C than healthy adults (50–60 years old). This study indicated that unsuccessful aging implies a greater oxidative stress than healthy aging, and that plasma antioxidants might predict both aging conditions.

Work by Cherubini et al. (2001) showed that increased levels of vitamins E in plasma combined with low LDL oxidation in octogenarians, are associated with the absence of atherosclerosis. In the same study, no protective role for lycopene or β-carotene was found.

3. Enzymatic antioxidants in humans

Despite the clear demonstration that humans have higher tissue superoxide dismutase concentration than short-living mammalian species (Cutler, 1991) little information on antioxidant enzymes concentration and/or activity in human aging is available in the literature. At variance, there are abundant reports on the level of antioxidant enzymes in experimental animals, mainly mice and rats. Although there is no absolute agreement, there is a sort of consensus in that the levels of superoxide dismutase, catalase and glutathione peroxidase of a series of tissues (liver, brain, kidney, heart, etc.) are decreased in senescent animals (Salminen et al., 1988; Cand and Verdetti, 1989; Navarro et al., 2004).

Concerning humans, Guemouri et al. (1991) found that superoxide dismutase was unchanged in subjects less than 65 years old and slightly decreased in the elderly. Similarly, glutathione peroxidase activity increases in younger adults, stabilizes in adults less than 65 years old, and declines in older persons (Artur et al., 1992). Andersen et al. (1997) studied the variability of several red blood cells antioxidant enzymes activities within a general Danish population (age 20–89) as caused by age, gender, and life-style factors, and found an age-related decrease in Cu, Zn-superoxide dismutase and glutathione reductase activity, together with no changes in the activities of glutathione peroxidase and catalase with increasing age.

According to Mecocci et al. (2000) plasma and red blood cell superoxide dismutase activities and plasma glutathione peroxidase activity, increase with increasing age. They concluded that senescence seems be associated with a decline in nutritional antioxidants together with an increase in antioxidant enzyme activity; the latter understood as an adaptive response to and increased level of oxidation products.

4. Products of lipid, DNA and protein oxidation

An increasing body of evidence provided by literature drives us to the concept that oxidation of biomolecules is related to susceptibility to diseases, such as cancer and heart disease, as well as associated with the process of aging. This issue has been recently revised by Cutler and Rodriguez (2003). Some markers of oxidative damage
to macromolecules, among them, thiobarbituric acid reactive substances (TBARS), alkenals, 8-isoprostane, 8-hydroxydeoxyguanosine, and protein carbonyls, have been commonly used for the last 20 years in human aging studies. Differently from common nutritional antioxidants, which are almost always measured by HPLC, the products of oxidative damage to lipids, DNA and proteins have shown analytical problems concerning techniques, sample collection, and relevance of the results for aging. After extensive reviewing, we found that the products derived from lipoperoxidation, as TBARS and malonaldehyde, despite all different markers that have been measured, are those that offer a more relevant bulk of data for the present review.

Mezzetti et al. (1996) showed that plasma peroxides, as measured by lipid peroxidation fluorescent products, is higher in elderly than in younger human subjects, and even higher in disabled octo-nonagenarians. This increase in lipid oxidation products was directly correlated with age, and was associated with decreases in vitamins E and C. The same analytical determination showed that lipid oxidation was higher in octogenarians with carotid atherosclerosis than in those with successful vascular aging (Cherubini et al., 2001). The authors concluded that high plasma vitamin E levels and low lipoperoxidation are predictors of absence of atherosclerosis in old subjects, suggesting that appropriate levels of vitamin E might be important for achieving successful vascular aging. In the EVA (Etude du Vieillissement Arteriel) study (Berr et al., 2000) plasma TBARS were measured together with some antioxidants to evaluate whether cognitive decline in the elderly is associated with systemic oxidative stress. Subjects with higher levels of TBARS have an increased risk of cognitive decline, this risk being even higher in those patients with low plasma selenium and carotenoids, and with low erythrocyte vitamin E levels.

Recent work from Block et al. (2003) evaluated the plasma levels of malondialdehyde (MDA), in order to get insight on the oxidative stress status in healthy people. The levels of MDA, measured using commercial kits (Oxis International Inc., Portland, OR), are strongly related to gender, as women have significantly higher MDA than men. No apparent relationship was found between MDA levels and age. One of the most striking results is that, after a univariate analysis of correlation, MDA showed a negative correlation with plasma ascorbic acid, α-tocopherol, γ-tocopherol, α-carotene, β-carotene, and β-cryptoxanthin. As the plasma levels of antioxidants correlate with each other, univariate analysis of a single variable at a time can be misleading. After a multivariate analysis, sex was the major predictor of high levels of MDA, as was plasma ascorbic acid in the inverse direction (Block et al., 2003). The mentioned study seems to tell us that a simple assay can be used as marker of oxidative stress in humans.

5. São Paulo oxidative stress and aging study (SPOSAS)

This study was designed to evaluate the plasma level of lipid oxidation products, the plasma concentration of nutritional antioxidants, and the activities of the antioxidant enzymes of red blood cells (Chan et al., 1998) in healthy humans of different ages. The studied group consisted of 503 healthy individuals, 48% male and 52%
female, aged from 20 to more than 70. The inclusion criteria for the study were: (1) negative history for cardiovascular, neurological, respiratory, or hepatic diseases, neoplasia, diabetes (type I or II), dementia, arthritis, major depression, alcoholism, and smoking habits, and (2) absence of pathologic values in blood clinical parameters. The participants were selected from an initial group of 2100 volunteers. At the end of the study, individuals meeting the above mentioned criteria were divided into smaller groups according to their ages: 20–29, 30–39, 40–49, 50–59, 60–69, and 70 and more years old. None of the subjects included in the study groups were taking vitamin supplements or any other pharmaceutical with antioxidant activity. A 3-day recall nutritional survey was conducted to estimate the daily intake of vitamin C, vitamin E, and β-carotene through the intake frequency of a list of 17 nutrients, the sources of nutritional antioxidants, and the eating habits of the selected individuals (Jelliffe and Jelliffe, 1989). The Medical Ethics Committee of the Brazilian Society of Orthomolecular Medicine approved this study and informed consent was signed by all participants. Blood samples were taken on heparin, after 12 h fasting. Plasma was separated from red blood cells by conventional centrifugation, was stored (maximum 48 h) for nutritional antioxidants (Gomes et al., 2004), and TBARS (Ohkawa et al., 1979) measurements. Red blood cells were processed for Cu, Zn-superoxide dismutase (McCord and Fridovich, 1969), catalase (Beutler, 1975), and glutathione peroxidase (Sies et al., 1979) activity measurements. Plasma cholesterol and lipid profile were determined (Technicon autoanalyser, model R4100) as reference for liposoluble antioxidants. The clinical values were grouped as means ± standard deviation. Significant differences between groups were determined by analysis of variance followed by Bonferroni’s test for multiple comparisons between independent groups. Correlation between variables was done using the Pearson correlation test. The level of significance was set up at $p < 0.05$ for all statistical analysis.

Levels of cholesterol (total, LDL-, HDL-, and VLDL-) and tryglicerides in the studied subjects were within normal and recommended levels (results not shown). The plasma concentration of TBARS increased significantly, 20–45%, in individuals of over 50 years of age, as compared with the 20–29 years group, that was taken as reference (Table 1). Linear regression of the data showed a positive and statistically significant correlation between age and TBARS levels ($r = 0.972$, $p < 0.01$). A similar increase in lipid oxidation products has been referred by other authors (Mezzetti et al., 1996; Cherubini et al., 2001; Block et al., 2003) but none of them showed correlation between increasing age and TBARS levels. It is worth noting that the linear correlation is conceptually in agreement with the notion of aging as a general and continuous decline of physiological and biochemical functions (Cutler, 1984). It is likely that the number of considered individual, sex, age groups, and inclusion and exclusion criteria are determinant in order to observe the correlation between age and plasma TBARS. A previous observation from our group, positively correlated age and oxidants production in stimulated neutrophils (Chan et al., 1998).

Although the daily intake of α-tocopherol was almost similar in the studied groups, with slightly (9%) increased intakes in subjects aged 40–69, we found marked differences in plasma α-tocopherol levels (Table 2). Progressively increasing plasma levels of α-tocopherol were found in groups from 20–29 years old to 50–59 years old,
where maximal levels were observed (66% increase), even when values were corrected for LDL cholesterol (Table 2). However, the oldest individuals, over 60 years old, showed levels of α-tocopherol than were even lower than those of younger subjects (30–59 years old); moreover, the oldest group (<70 years) showed a level lower than

Table 1
Plasma lipoperoxidation products, measured as TBARS, in aging humans

<table>
<thead>
<tr>
<th>Group</th>
<th>Age interval (years)</th>
<th>TBARS (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20–29 (57)</td>
<td>2.0 ± 0.1</td>
</tr>
<tr>
<td>2</td>
<td>30–39 (74)</td>
<td>2.3 ± 0.1</td>
</tr>
<tr>
<td>3</td>
<td>40–49 (115)</td>
<td>2.3 ± 0.1</td>
</tr>
<tr>
<td>4</td>
<td>50–59 (110)</td>
<td>2.4 ± 0.1</td>
</tr>
<tr>
<td>5</td>
<td>60–69 (69)</td>
<td>2.5 ± 0.1</td>
</tr>
<tr>
<td>6</td>
<td>≥ 70 (32)</td>
<td>2.9 ± 0.3</td>
</tr>
</tbody>
</table>

*p < 0.05.

* Different from group 1.

\text{α} \text{Tocopherol}

<table>
<thead>
<tr>
<th>Group</th>
<th>Age interval (years)</th>
<th>α-Tocopherol</th>
<th>Daily intake (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20–29</td>
<td>21.0 ± 0.8</td>
<td>11.9 ± 0.1</td>
</tr>
<tr>
<td>2</td>
<td>30–39</td>
<td>26.2 ± 1.1</td>
<td>12.1 ± 0.1</td>
</tr>
<tr>
<td>3</td>
<td>40–49</td>
<td>29.0 ± 1.2</td>
<td>12.8 ± 0.1</td>
</tr>
<tr>
<td>4</td>
<td>50–59</td>
<td>34.9 ± 1.5</td>
<td>13.6 ± 0.1</td>
</tr>
<tr>
<td>5</td>
<td>60–69</td>
<td>30.9 ± 1.1</td>
<td>12.7 ± 0.1</td>
</tr>
<tr>
<td>6</td>
<td>≥ 70</td>
<td>22.2 ± 2.1</td>
<td>12.4 ± 0.1</td>
</tr>
</tbody>
</table>

\text{β-Carotene}

<table>
<thead>
<tr>
<th>Group</th>
<th>Age interval (years)</th>
<th>β-Carotene</th>
<th>Daily intake (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20–29</td>
<td>1.00 ± 0.1</td>
<td>2.90 ± 0.02</td>
</tr>
<tr>
<td>2</td>
<td>30–39</td>
<td>1.10 ± 0.1</td>
<td>2.78 ± 0.01</td>
</tr>
<tr>
<td>3</td>
<td>40–49</td>
<td>1.31 ± 0.04</td>
<td>3.01 ± 0.02</td>
</tr>
<tr>
<td>4</td>
<td>50–59</td>
<td>1.15 ± 0.06</td>
<td>2.88 ± 0.03</td>
</tr>
<tr>
<td>5</td>
<td>60–69</td>
<td>1.10 ± 0.03</td>
<td>2.79 ± 0.20</td>
</tr>
<tr>
<td>6</td>
<td>≥ 70</td>
<td>0.85 ± 0.02</td>
<td>2.68 ± 0.12</td>
</tr>
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\text{Ascorbic acid}

<table>
<thead>
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<th>Group</th>
<th>Age interval (years)</th>
<th>Ascorbic acid</th>
<th>Daily intake (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20–29</td>
<td>56 ± 3</td>
<td>167 ± 3</td>
</tr>
<tr>
<td>2</td>
<td>30–39</td>
<td>54 ± 3</td>
<td>168 ± 9</td>
</tr>
<tr>
<td>3</td>
<td>40–49</td>
<td>51 ± 3</td>
<td>160 ± 10</td>
</tr>
<tr>
<td>4</td>
<td>50–59</td>
<td>50 ± 4</td>
<td>158 ± 12</td>
</tr>
<tr>
<td>5</td>
<td>60–69</td>
<td>58 ± 4</td>
<td>153 ± 10</td>
</tr>
<tr>
<td>6</td>
<td>≥ 70</td>
<td>51 ± 5</td>
<td>148 ± 12</td>
</tr>
</tbody>
</table>

*p < 0.05. Groups as in Table 1.

* Different from group 1.

\text{β-Carotene}

* Different from group 2.

* Different from group 5.

Table 2
Plasma levels and daily intake of α-tocopherol, β-carotene and ascorbic acid in aging humans

<table>
<thead>
<tr>
<th>Group</th>
<th>Age interval (years)</th>
<th>α-Tocopherol</th>
<th>β-Carotene</th>
<th>Ascorbic acid</th>
<th>Daily intake (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20–29</td>
<td>21.0 ± 0.8</td>
<td>1.00 ± 0.1</td>
<td>56 ± 3</td>
<td>167 ± 3</td>
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<td>≥ 70</td>
<td>22.2 ± 2.1</td>
<td>0.85 ± 0.02</td>
<td>51 ± 5</td>
<td>148 ± 12</td>
</tr>
</tbody>
</table>
the one of the youngest age (20–29 years) group, when tocopherol concentration was corrected for LDL-cholesterol (Table 2). Controversial results have been reported about the correlation between plasma α-tocopherol and the vitamin E intake (reviewed by Blumberg and Halpner, 1999). Herbeth et al. (1989) reported a significant correlation between recorded dietary intake and measured plasma levels of vitamin E in older adults but did not differentiate between supplements users and nonusers. It is well known that this correlation is true when vitamin E supplements are taken. Data from literature show that plasma α-tocopherol appears to be increased with age in most longitudinal (Haller et al., 1996; Öhrvall et al., 1996) and cross-sectional studies (Battisti et al., 1994; Hallfrisch et al., 1994; Borel et al., 1997; Winklhofer-Roob et al., 1997). In some cases, the increase is limited to women (Ascherio et al., 1992) or to middle-aged subjects (Knert et al., 1988). Few studies found no effect of age (Morinobu et al., 1994; Alberti-Fidanza et al., 1995) or even a decrease in plasma α-tocopherol concentrations with age (Vatassery et al., 1983; Mino et al., 1993).

The behavior of plasma β-carotene levels was quite similar to that of α-tocopherol (Table 2). Although slight (4–8%) differences were found in the intake of β-carotene between all studied subjects, the plasma levels of the carotene significantly increased, 31%, from the younger (20–29 years) to the middle-aged group (40–49 years), and decreased in the oldest groups. It is worth mentioning that the oldest groups had a plasma β-carotene referred to LDL cholesterol that was lower than the one of the youngest group (Table 2). The status of β-carotene in aging humans is another point of disagreement in the literature (Blumberg and Halpner, 1999). An example of confounding results arises from the Dietary and Nutritional Survey of British Adults that showed a slight increase in serum α-carotene from young to middle age, and a significant increase in β-carotene with age. Järvinen et al. (1993) also noted that confounding results might occur if β-carotene is measured in plasma of non-fasting subjects. Ascherio et al. (1992) reported a significant relationship between estimated intake and plasma levels of β-carotene.

Discrepancies and the absence of correlation between plasma levels and intake of α-tocopherol and β-carotene found in this study are likely due to the inaccuracy of nutritional surveys, mainly for these antioxidants (Block et al., 2001; Hegsted, 1997). Moreover, the discrepancy between intake and plasma levels of both liposoluble vitamins is more marked in the elderly groups. This may be explained by different composition in dietary fat, impairment of vitamin absorption, and different fat dynamics in the elderly.

Levels of plasma vitamin C were not significantly different among all the studied groups (Table 2) as well as the daily intake of the vitamin. These data are in disagreement with previous reports by Paolisso et al. (1998), Mecocci et al. (2000) and Mezzetti et al. (1996) who showed a decrease in plasma vitamin C associated to increasing age. Nevertheless, none of the mentioned studies evaluated the intake of the vitamins to ensure that the decrease in plasma levels was not due to a decreased intake.

The activities of the red blood cell antioxidant enzymes, Cu, Zn-superoxide dismutase and catalase, were not modified by age. On the other hand, glutathione peroxidase activity showed a direct and significant correlation with increasing age \( (r = 0.986, p < 0.0001) \) (Table 3). Moreover, glutathione peroxidase activity strongly
correlates with the plasma levels of TBARS ($r = 0.957, p < 0.01$). Could this increase in glutathione peroxidase activity be understood as a compensatory effect for lower nutritional antioxidants and increased plasma lipoperoxidation products? The dependence follows a known adaptive response of glutathione peroxidase activity in organs exposed to increased levels of oxidized lipids (Chance et al., 1979). In view of the strong correlation between plasma TBARS and red blood cell glutathione peroxidase activity, we suggest that, in the elderly, glutathione peroxidase may play a role in controlling oxidative stress. Moreover, red blood cell glutathione peroxidase activity can be used as a marker of oxidative stress in old human subjects.

6. Concluding remarks

In conclusion, data revised and presented here allow us to argue that aging is a process directly related to systemic oxidative stress. Two components of the oxidative stress situation have been recognized in human aging: a decrease in availability of nutritional molecular antioxidants and an accumulation of products derived from the oxidation of biological structures. Moreover, aging cells and tissues are likely to counteract the decrease in nutritional antioxidants by increasing the amount and/or activity of antioxidant enzymes, as observed with red blood cells glutathione peroxidase, the antioxidant enzyme responsible for the metabolism of a variety of hydroperoxides. Supplementation studies with antioxidant vitamins are necessary to understand whether it is possible to provide healthy aging to the population, decreasing the occurrence of age-related diseases.

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