ANTIOXIDANTS & REDOX SIGNALING
Volume 8, Numbers 3 & 4, 2006
© Mary Ann Liebert, Inc.

Forum Review

Oxidative Damage and Platelet Activation as New Predictors of Mobility Disability and Mortality in Elders

MATTEO CESARI,[1] STEPHEN B. KRITCHEVSKY,[2]
CHRISTIAAN LEEUWENBURGH,[1] and MARCO PAHOR[1]

ABSTRACT

Mobility disability is an early phase of the disablement process in older adults, and represents a major risk factor for physical disability and mortality. Pathophysiological mechanisms responsible for the onset of mobility limitation are still largely unknown. Oxidative damage, responsible for the disruption of the equilibrium of biological systems by damaging major constituent molecules, might play an important role in the pathway leading to major health-related events. It has been suggested the existence of a vicious cycle involving oxidative damage, platelet activation, and inflammation as promoter of pathophysiological changes occurring with aging. This hypothesis is based on the following observations: (a) oxidative damage is associated with diseases and clinical conditions potentially leading to disability and mortality; (b) oxidative damage is associated with platelet activation, and a vicious cycle involving oxidative damage, platelet activation, and inflammation has been demonstrated in several metabolic disorders potentially leading to mobility disability; (c) the age-related physical decline may be associated to the oxidative damage due to the excess of free radicals; (d) antioxidant defense and behavioral factors (e.g., physical activity, dietary restriction, smoking cessation) play an important role in the reduction of oxidative damage levels and are associated with improved physical performance and muscle strength. *Antioxid. Redox Signal.* 8, 609–619.

INTRODUCTION

A PRIMARY GOAL of health care for older persons is to maintain physical function. Mobility limitation represents a major risk factor for physical disability, which is associated with worse quality of life, increased risk for mortality, hospitalization, need for long-term care, and higher health care costs (33).

In the 1950s, Harman hypothesized the "free radical theory" of aging, suggesting that endogenous oxygen radicals generated in normal cellular processes resulted in cumulative oxidative damage (43), which produces aging-related changes that exponentially increase the chance of death with advancing age, even under optimal living conditions (44). Oxidative damage has been associated with platelet activation (16, 18–22) and inflammation (30, 42, 55, 60, 105, 110). A vicious cycle involving these three mechanisms and playing an important role in the development and progression of several metabolic disorders has been suggested (21, 22). Moreover, current evidence show that oxidative damage may represent a potential explanation for the pathophysiological changes occurring during the aging process (28, 70, 90). Mobility disability and mortality might represent the final outcomes of this mechanism. In the present review paper, we propose that a vicious cycle involving oxidative damage, platelet activation, and inflammation may promote pathophysiological changes leading to mobility disability and mortality (Fig. 1).

[1]Department of Aging and Geriatric Research, College of Medicine, Institute on Aging, University of Florida, Gainesville, Florida, USA.
[2]Sticht Center on Aging, Wake Forest University School of Medicine, Winston Salem, North Carolina, USA.

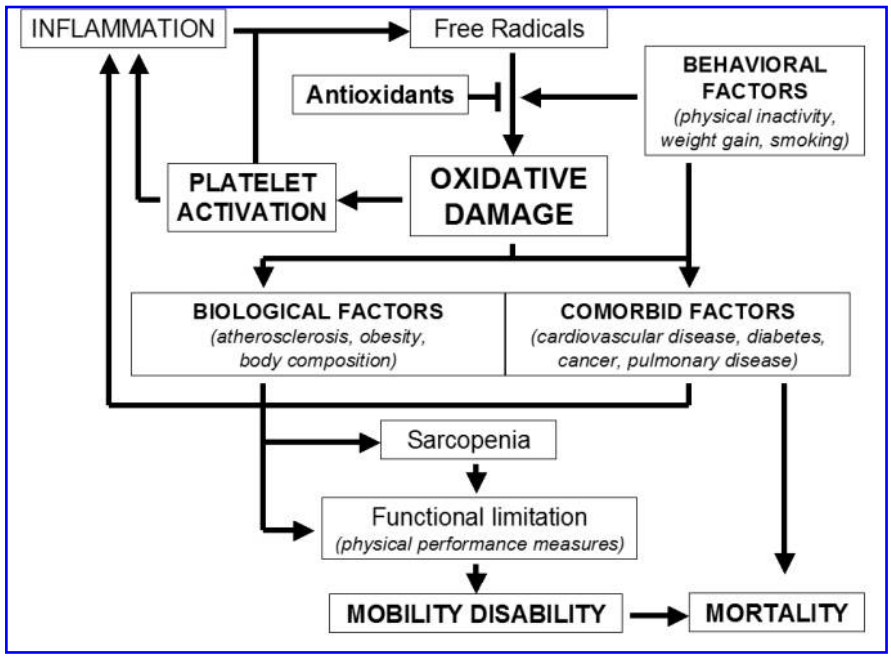

FIG. 1. Oxidative damage, mobility disability and mortality.

8-ISO-PROSTAGLANDIN $F_{2\alpha}$ (8-ISO-$PGF_{2\alpha}$) AND LIPID PEROXIDATION

Most of the current evidence exploring the pathophysiological effects of oxidative stress are based on lipid damage. Lipid peroxidation represents a risk factor for several biological conditions and clinical diseases potentially leading to the onset of mobility disability and mortality.

The 8-iso-$PGF_{2\alpha}$ is a member of a family of prostaglandin isomers called *F_2-isoprostanes*. In contrast to classic prostaglandins, formed through an enzymatic action of the prostaglandin H synthase from arachidonic acid, F_2-isoprostanes result from a free radical-catalyzed mechanism (79), thus providing an optimal estimate of oxidative damage to cellular lipids (77). The formation of isoprostanes in lipid bilayers may contribute to alterations in fluidity and integrity of cellular membranes (80, 99).

Isoprostanes have been detected in fresh and stored samples of plasma and urine (4, 79), but also in cerebrospinal (39), pericardial (66), bronchoalveolar (74), and amniotic fluids (63). The finding of detectable levels of F_2-isoprostanes in all normal animal and human biological fluids and esterified in normal animal tissues indicates that there is ongoing lipid peroxidation that is incompletely suppressed by antioxidant defenses, even in nondiseased individuals (62). Isoprostane levels do not exhibit diurnal variations (47), but do vary markedly in clinical and experimental conditions characterized by oxidative stress, and these values closely parallel disease severity (52). Lipid peroxidation has consistently shown to be strongly associated with platelet activation and inflammation, so that it has been hypothesized the presence of a vicious cycle between these three mechanisms (Fig. 1) (21, 22).

Other measures of lipid peroxidation can be currently assessed, but the measurement of 8-iso-$PGF_{2\alpha}$ is superior as an index of lipid peroxidation to other measurements. F_2-isoprostanes derive only from arachidonic acid, while malondialdehyde is generated by other fatty acids with different peroxidation rates at different O_2 tensions based on the number of double bonds contained in the molecule (64). Oxidized LDL (oxLDL) represent a well-established cardiovascular risk factor commonly adopted to measure oxidative damage, in particular lipoprotein peroxidation. F_2-isoprostanes are formed during the oxidative modification of LDL and, consequently, represent earlier markers of oxidative damage compared to oxLDL (75). Moreover, the predictive value for the onset of mobility disability and mortality of oxLDL levels, which are measured in blood, might only be due to the atherogenic action and consequent cardiovascular status associated with this lipoprotein peroxidation marker. In contrast from oxLDL, F_2-isoprostanes have been found in several and different tissues and body fluids (4, 39, 63, 66, 74, 79). This suggests that 8-iso-$PGF_{2\alpha}$ may represent an excellent biomarker of lipid peroxidation for aging studies and, through its multisystemic effects, play an important role in the disabling process.

OXIDATIVE DAMAGE, PLATELET ACTIVATION, AND INFLAMMATION CONSTITUTE A VICIOUS CYCLE

8-iso-$PGF_{2\alpha}$, a marker of lipid peroxidation, is able to induce a dose-dependent platelet activation (21, 80, 99). In fact, the reported linear relationship between 8-iso-$PGF_{2\alpha}$ and 11-dehydro-thromboxane B_2 (11-dehydro-TXB_2), a well-established and reliable marker of platelet activation, suggests the isoprostanes may be responsible for cellular

activation (21). The association between the 8-iso-$PGF_{2\alpha}$ and 11-dehydro-TXB_2 levels has been demonstrated in pro-inflammatory conditions, such as in obesity (22), in patients with hypercholesterolemia (16), diabetes mellitus (19), and homozygous homocystinuria (20). Therefore, the underlying inflammatory state associated with these metabolic disorders may be the primary trigger of a TX-dependent platelet activation mediated, at least in part, through enhanced lipid peroxidation (21). A direct relationship between inflammatory markers and 8-iso-$PGF_{2\alpha}$ has also been shown (30, 42, 55, 60, 105, 110), supporting the hypothesis of a vicious cycle involving oxidative damage, platelet activation, and inflammation. Several feed-forward mechanisms amplifying and sustaining the cycle composed by inflammation, oxidative damage, and platelet activation have also been demonstrated, such as the effects of F_2-isoprostanes on inflammatory gene expression (69), the synthesis and release of inflammatory cytokines from activated platelets (61), and a direct proinflammatory effect of C-reactive protein (CRP) (91). Finally, increasing evidence is supporting an extensive cross-talk between inflammation and coagulation, in which inflammation leads to activation of coagulation and this latter can modulate inflammatory activity (59).

ANTIOXIDANT DEFENSE COUNTERBALANCES THE EFFECTS OF THE OXIDATIVE DAMAGE

An ideal "golden triangle" of oxidative balance, in which oxidants, antioxidants, and biomolecules are placed at each apex, has been described (11). In a normal situation, a balanced equilibrium exists among these three elements. Excess generation of free radicals may overwhelm natural cellular antioxidant defenses leading to lipid peroxidation and further contributing to muscle damage. Also noteworthy is the increasing evidence reporting the strong relationship between antioxidants and platelet activation (19–21, 83, 96).

Vitamin C is a water-soluble vitamin representing a first-line antioxidant defense in plasma. It is a powerful inhibitor of lipid peroxidation and regenerates vitamin E in lipoproteins and membranes. A strong inverse association has been shown between plasma ascorbic acid and F_2-isoprostanes (10). Bagi *et al.* (5) have shown that chronic vitamin C treatment is able to decrease high levels of 8-iso-$PGF_{2\alpha}$ in animal models.

Vitamin E is a lipid-soluble vitamin found in cell membranes and circulating lipoproteins. It protects against lipid peroxidation by acting directly with a variety of oxygen radicals. Its antioxidant function is strongly supported by regeneration promoted by vitamin C (67). Vitamin E is thought to have a role in the prevention of atherosclerosis through inhibition of oxidative modifications of LDLs (112, 119). The formation of F_2-isoprostanes increases significantly in animals deficient in vitamin E (82). Moreover, inhibition of isoprostanes formation by vitamin E supplementation has been shown in humans (114) as well as in animal models (62).

Carotenoids are lipid-soluble antioxidants. Plasma levels of carotenoids are negatively correlated with levels of F_2-isoprostanes (10). Carotenoids levels are inversely associated with inflammation (50), atherosclerosis (101), cardiovascular disease (36), sarcopenia (107), and mortality (50), and positively correlated with physical performance (14). Improvements in antioxidant status and reduction of lipid peroxidation have been shown after carotenoids supplementation (114).

Vitamin C, vitamin E, and carotenoids have shown to interact synergistically against lipid peroxidation (86). Higher serum levels of antioxidants are associated with higher strength and physical performance measures (14, 107), suggesting that oxidative damage may play an important role for the onset of mobility disability.

OXIDATIVE DAMAGE, INFLAMMATION, AND PLATELET ACTIVATION ARE ASSOCIATED WITH PATHOPHYSIOLOGICAL CONDITIONS POTENTIALLY LEADING TO THE ONSET OF MOBILITY DISABILITY AND MORTALITY

Some physiological changes occurring with aging and associated with mobility disability and mortality have been related to the accumulation of oxidative damage (70).

A graded relationship between the extent of vascular disease and the likelihood of maintaining intact mobility function has previously been demonstrated (85). Isoprostanes have been indicated as important markers of the atherosclerotic process (77, 94). Oxidation of LDL, responsible for the formation of foam cells in the vascular wall, results in a significantly higher isoprostane synthesis (65, 98). In ApoE-deficient mice, levels of isoprostane are increased compared to controls (100). On the other hand, plasma levels of vitamin C, vitamin E, and β-carotene are inversely associated with carotid atherosclerosis (35), supporting the hypothesis of a relationship between antioxidants (and consequently oxidative damage) and atherosclerosis. The important role played by platelet activation during the atherogenesis has been widely demonstrated (93).

Oxidative damage and platelet activation are also associated with inflammation (18, 22, 30, 42, 55, 59–61, 69, 91, 105, 110), which, on the other hand, is able to affect skeletal muscle mass and quality, namely by accelerating changes that are typical of the aging process (1, 29). A direct influence of cytokine levels on muscle mass has been demonstrated in humans (1, 45) as well as in animal models (49). Moreover, the predictive value of inflammatory markers for the onset of mobility limitation and mortality in older persons has already been extensively demonstrated (15, 29, 116).

Obesity, a major risk factor for disability and mortality, is positively associated with oxidative damage (10, 22, 23, 53) and platelet activation (22). Moreover, obesity is associated with insulin resistance, and emerging evidence links insulin resistance to oxidative stress (26). Obese subjects present higher levels of inflammatory markers (12, 120). Therefore, body composition measures and obesity might represent im-

portant mediators in the pathway leading from oxidative damage to the onset of mobility disability and mortality.

OXIDATIVE DAMAGE, INFLAMMATION, AND PLATELET ACTIVATION ARE ASSOCIATED WITH DISEASES POTENTIALLY LEADING TO THE ONSET OF MOBILITY DISABILITY AND MORTALITY

The burden of comorbidity has been defined as an etiological risk factor for the frailty syndrome, which has disability as major outcome. It has been shown that oxidative damage, inflammation, and platelet activation are associated to several clinical conditions.

In the cardiovascular system, lipids are in the first line of free radical attack. Increasing evidence is indicating isoprostanes as markers of atherosclerotic diseases (94). Established risk factors for coronary heart disease are associated with elevated levels of isoprostanes (16, 19, 22, 72, 78). Markers of lipid peroxidation and platelet activation are significantly increased in human essential hypertension (72, 73). Moreover, higher levels of F_2-isoprostanes and inflammatory markers, together with lower levels of vitamin C, have been demonstrated in stroke patients (105). Strong associations between platelet activation and atherosclerotic clinical conditions have been widely documented as well (93). Urinary levels of 11-dehydro TXB_2 are increased in patients with stroke (68) and hypertension (72, 73), and are able to predict myocardial infarction and cardiovascular death (25).

The association of diabetes, a risk factor for lower extremity limitation (115), with enhanced lipid peroxidation and platelet activation is well established (18, 19, 48, 62, 104). The formation of F_2-isoprostanes is induced in vascular smooth muscle cells *in vitro* by elevated glucose concentrations (84). Plasma concentrations of 8-epi-$PGF_{2\alpha}$ increase during acute hyperglycemia in diabetic patients (104).

Even if DNA oxidative damage seems to be more important for pathophysiological cellular changes leading to the onset of cancer, it is reasonable that these modifications might lead to fatal changes of cellular architecture. It has been shown that estrogen-induced carcinogenesis is associated with higher levels of 8-iso-$PGF_{2\alpha}$ (9). Lipid peroxidation has also been indicated as responsible of promutagenic lesions potentially leading to colon carcinogenesis (89). Increased levels of 11-dehydro-TXB_2 urinary excretion have been found in patients with colorectal cancer (106) and systemic mastocytosis (81).

Oxidative damage is involved in the pathophysiology of several pulmonary conditions, which are also associated with an increased risk of mobility disability (87). Isoprostanes, which are potent constrictors of pulmonary vascular smooth muscle and airway smooth muscle (52), are produced by free radicals released by inflammatory cells in the airways and by virtually every cell type in the lungs (52). Increased levels of F_2-isoprostanes have been reported in patients with allergic asthma (24) and in expired breath condensate of patients with chronic obstructive pulmonary disease (COPD) (54). Platelet activation is enhanced in patients with COPD and asthma (17, 57). It has been suggested that the enhanced thromboxane biosynthesis may be due to changes in the arterial oxygen tension (17).

Finally, free radicals, and consequent oxidative damage, have been indicated, at least in part, as key factors to brain aging (27). It has also been shown that cerebrospinal fluid and brain tissue levels of isoprostane are increased in several neurodegenerative diseases, such as Alzheimer's disease (38).

OXIDATIVE DAMAGE, INFLAMMATION, AND PLATELET ACTIVATION ARE ASSOCIATED WITH BEHAVIORAL FACTORS POTENTIALLY LEADING TO THE ONSET OF MOBILITY DISABILITY AND MORTALITY

Some behavioral factors have shown to potentially mediate between oxidative damage and onset of mobility disability and mortality (113). Cigarette smoke is characterized by a number of oxidizing species, capable of producing lipid peroxidation (32). The relationship between smoking and isoprostane levels is widely demonstrated (62, 78, 92, 102). Consistent with this notion, smokers typically show reduced levels of antioxidants, such as vitamin C (31). Quitting smoking and antioxidant vitamin therapy are able to reduce elevated levels of 8-epi-$PGF_{2\alpha}$ in chronic smokers (102). Smoking has also been associated with increased levels of platelet activation and inflammation (51, 92).

Physical activity may play an important role in limiting the free radical production and oxidative damage. Even if exercise is associated with an abnormal production of free radicals, the elderly who are physically active benefit from exercise-induced adaptations in the cellular antioxidant defense systems (34). Physical exercise training has also shown to reduce basal levels of thromboxane in animal models (2).

Weight loss improves physical performance and function in older adults (71). On the other hand, weight changes are positively associated with oxidative damage, platelet activation, and inflammation (22).

ANTIOXIDANT SUPPLEMENTATION

Several studies have reported a reduction in lipid peroxidation and platelet activation after antioxidant supplementation (16, 19, 23, 102). However, whether higher antioxidant intake is beneficial in promoting better physical performance and muscular strength is still controversial. Although findings of some studies have shown improvements (46, 114, 118), other studies do not support a beneficial effect of increased antioxidant intakes on physical performance (3, 6, 7, 88). Nevertheless, it seems reasonable that an adequate antioxidant intake is needed to maintain healthy muscular activity (67). These controversial results might be explained by the need of better targeting of subjects who can benefit from antioxidant supplementation (56). It is likely that only subjects with a low antioxidant status (due to an inadequate antioxi-

dant intake) or those with high levels of oxidative damage should be candidates for an antioxidant supplementation. To address this issue, it is also needed to better explore the relationship of dietary antioxidants intake with oxidative damage, platelet activation, inflammation, and serum antioxidants levels. The antioxidant intake may not only be associated with serum antioxidants levels, but also inversely associated with levels of oxidative damage, platelet activation, and inflammatory markers. This hypothesis needs to be confirmed, since it might provide the basis for future intervention studies aimed to evaluate whether diet or antioxidant supplementation are able to reduce oxidative damage, platelet activation, and inflammation.

OXIDATIVE DAMAGE, INFLAMMATION, PLATELET ACTIVATION, SARCOPENIA, AND THE AGE-RELATED PHYSICAL PERFORMANCE LOSS

Sarcopenia is a key factor in the pathway leading from the biological and clinical mediators linked to the oxidative damage and platelet activation to the onset of mobility disability (Fig. 1). Sarcopenia, defined as the involuntary loss of skeletal muscle occurring with advancing age, results in a decrease of muscular strength and endurance and is associated with a loss of autonomy in older persons (76). Several studies have suggested that oxidative damage might be responsible for this muscle strength and stamina reduction (14, 28, 70, 90). The relationship between inflammation and sarcopenia is widely demonstrated (76).

MECHANISMS LINKING OXIDATIVE DAMAGE TO SARCOPENIA

Lipid peroxidation in membranes is extremely important for proper cellular function. Phospholipids in membranes represent a major site for the generation of reactive oxygen species because of its high content of polyunsaturated fatty acids. The allylic hydrogens in polyunsaturated fatty acids are extremely sensitive to free radicals; this sensitivity leads to lipid peroxidation and the generation of peroxyl radicals. At the same time, the peroxyl radicals are capable of abstracting allylic hydrogens from other fatty acids to produce more lipid hydroperoxides, generating consequently a chain reaction of lipid peroxidation (41).

Lipid peroxidation decreases membrane fluidity and increases the leakiness of the membrane bilayer to substances that do not normally cross the membrane other than through specific channels (103, 117). Lipid peroxidation can also produce cytotoxic compounds able to inhibit protein and DNA synthesis and toxic to mitochondria. Continued oxidation of fatty acid side-chains and their fragmentation to produce aldehydes and hydrocarbons will eventually lead to loss of membrane integrity. For example, rupture of the membranes of lysosomes can release hydrolytic enzymes into the cell, causing an amplification of the damage (41). In addition, lipid peroxidation can cause cross-linking and inactivation of membrane proteins (103, 117).

To date, no study has yet explored what is the role played by lipid peroxidation in mechanisms leading to sarcopenia. However, the cellular modifications associated with the age-related lipid peroxidation is likely to affect the skeletal muscle, limiting its functionality.

Besides these structural modifications potentially responsible for the loss of skeletal muscle, it is noteworthy that oxidative damage may lead to sarcopenia through other different proteolytic pathways (Fig. 2). In fact, a growing importance has been attributed to Ca^{2+}-activated proteases and the proteasome system (97).

Calpains (calpain I and II) are Ca^{2+}-dependent cysteine proteases responsible for the cleavage of cytoskeletal proteins (e.g., titin and nebulin) that anchor the muscle fiber contractile elements. The role played by calpains in the initial degradation of myofibrillar proteins occurring in muscle atrophy as well as in the necrosis process related to muscular dystrophies is well documented (8). Calpain activity is particularly enhanced by any factor elevating cytolosic calcium concentrations and/or decreases calpastatin levels (37). It has been suggested that oxidative damage may be responsible for cellular ionic disturbances, reducing plasma membrane Ca^{2+} ATPase activity (109). This would delay the removal of intracellular Ca^{2+}, promoting its accumulation (97). Moreover, there is evidence that cytolosic Ca^{2+} levels increase with age (111).

Caspases (*cy*steine-dependent, *aspar*tate-specific protea*ses*) represent a novel group of endoproteases which are responsible for cellular apoptosis through the protein degradation. In the cell, they are expressed as inactive precursors (i.e., procaspases). Procaspases can be activated into caspases (which will serve as apoptotic effectors, e.g., capsase-3) through mitochondrial- (i.e., release of cytochrome-c from the mitochondria forming an "apoptosome" which activates procaspase-9) and receptor- (i.e., apoptosis induced by tumor necrosis factor-α binding with its death receptor and activation of procaspase-8) mediated pathways. Moreover, the stress-related release of calcium from the endoplasmic reticulum into the cytosol is associated with a close cross-talk between the calpain and procaspase proteolytic systems (58, 97).

It has also been suggested that oxidative damage may accelerate muscle protein breakdown via 20S core proteasome (97). This latter is part of the 26S proteasome (together with a regulatory 19S complex). The 19S regulatory complex plays an important role in the ATP-dependent degradation of ubiquitinated proteins by removing the polyubiquitin chain and unfolding the substrate protein. The unfolded protein is then degraded into the 20S core without ATP. Moreover, the 20S core proteasome can selectively and independently degrades oxidatively modified proteins without ubiquitination (40).

Unfortunately, these proteolytic pathways associated with oxidative damage and potentially leading to sarcopenia are still too expensive and difficult to be assessed in large-scale studies. However, their use is extremely promising and likely to expand in the future. At this time, the use of lipid peroxidation markers (such as isoprostanes) may represent a more feasible means to assess the relationships between oxidative damage and health-related outcomes, especially for those events that, for their relatively low incidence, may need a large sample size to be adequately explored.

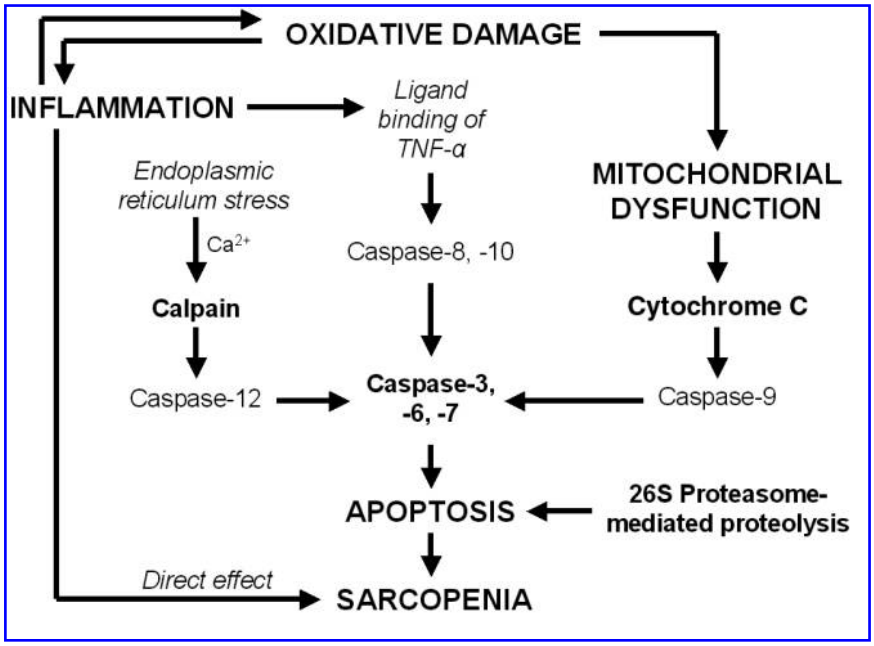

FIG. 2. Oxidative damage-related mechanisms leading to sarcopenia.

MECHANISMS LINKING PLATELET ACTIVATION TO SARCOPENIA

According to our knowledge, no studies have yet explored the relationship between platelet activation and sarcopenia. Nevertheless, it can be hypothesized that platelet activation may be associated with sarcopenia on the basis of previous studies showing (a) the association of sarcopenia with oxidative damage and inflammation, and (b) the relationship between these latter and platelet activation. An intervention program aimed at evaluating the beneficial effects of long-term aspirin supplementation in terms of life span extension is currently ongoing (95). In fact, aspirin has shown to affect oxidant production and cytokine responses, and to block glycooxidation reactions. Aspirin represents a highly attractive therapy to prevent age-related pathophysiological modifications due to its antiinflammatory, antithrombotic, antipyretic, analgesic, and antioxidant properties (95, 108). Therefore, aspirin may prevent the increase of the proinflammatory component of aging while reducing levels of oxidative damage. However, further studies are needed to confirm these hypotheses and evaluate the preventive role of antiplatelet treatment on health-related outcomes in the elderly.

OXIDATIVE DAMAGE, INFLAMMATION, AND PLATELET ACTIVATION ARE PREDICTORS OF MOBILITY DISABILITY AND MORTALITY

In a recent study (13), we explored the predictive value of oxidative damage (defined as plasma levels of oxLDL) for the onset of mobility limitation in the Health Aging and Body Composition. Levels of oxLDL were significantly associated with the incidence of mobility limitation, even after adjustment for potential confounders. This relationship was not driven by the presence of atherosclerotic diseases or other clinical conditions potentially mediating the relationship between lipid peroxidation and mobility limitation. These preliminary results are strongly supportive of our hypothesis of a relationship between oxidative damage and mobility disability. Moreover, even if commonly used, oxLDL do not represent the best marker of lipid peroxidation. In fact, F_2-isoprostanes are formed during the oxidative modification of LDL and, consequently, represent earlier markers of oxidative damage compared to oxLDL (75).

On the basis of current evidence, oxidative damage, strongly correlated with platelet activation and inflammation, may represent a possible trigger for the cascade leading to the onset of mobility disability and mortality. Along this pathway, biological and behavioral factors, as well as the burden of comorbidity (all are strongly linked to the oxidative damage) may serve as mediators for skeletal muscle and physical performance loss.

CONCLUSION

Pathophysiological mechanisms responsible for the onset of mobility limitation in older persons are still largely unknown. Future studies should be aimed to explore whether markers of oxidative damage and platelet activation are independent predictors of mobility disability and mortality. If this relationship will be demonstrated by future studies, several different goals of clinical utility will be reached:

- A pathophysiological mechanism will be recognized as promoter and responsible of the disabling process;
- Biological markers identifying older persons at high risk of disability events and mortality will be identified;

- New potential targets for future intervention for disability and mortality will be provided.

Further studies should also verify whether interventions aimed to reduce or prevent oxidative damage and platelet activation could be addressed for the prevention of disability and the increase of life expectancy in older persons.

ABBREVIATIONS

ATPase, adenosine triphosphatase; Ca^{2+}, calcium; Caspases, cysteine-dependent, aspartate-specific proteases; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; 8-iso-$PGF_{2\alpha}$, 8-iso-Prostaglandin $F_{2\alpha}$; 11-dehydro-TXB_2, 11-dehydro-thromboxane B_2; LDL, low density lipoprotein; oxLDL, oxidized LDL.

REFERENCES

1. Anker SD, Ponikowski PP, Clark AL, Leyva F, Rauchhaus M, Kemp M, Teixeira MM, Hellewell PG, Hooper J, Poole-Wilson PA, and Coats AJS. Cytokines and neurohormones relating to body composition alterations in the wasting syndrome of chronic heart failure. *Eur Heart J* 20: 683–693, 1999.
2. Arvola P, Wu X, Kahonen M, Makynen H, Riutta A, Mucha I, Solakivi T, Kainulainen H, and Porsti I. Exercise enhances vasorelaxation in experimental obesity associated hypertension. *Cardiovasc Res* 43: 992–1002, 1999.
3. Avery NG, Kaiser JL, Sharman MJ, Scheett TP, Barnes DM, Gomez AL, Kraemer WJ, and Volek JS. Effects of vitamin E supplementation on recovery from repeated bouts of resistance exercise. *J Strength Cond Res* 17: 801–809, 2003.
4. Awad JA, Morrow JD, Takahashi K, and Roberts LJ. Identification of non-cyclooxygenase-derived prostanoid (F2-isoprostane) metabolites in human urine and plasma. *J Biol Chem* 268: 4161–4169, 1993.
5. Bagi Z, Cseko C, Toth E, and Koller A. Oxidative stress-induced dysregulation of arteriosal wall shear stress and blood pressure in hyperhomocysteinemia is prevented by chronic vitamin C treatment. *Am J Physiol Heart Circ Physiol* 285: H2277–H2283, 2003.
6. Balakrishnan SD and Anuradha CV. Exercise, depletion of antioxidants and antioxidant manipulation. *Cell Biochem Funct* 16: 269–275, 1998.
7. Barnett DW and Conlee RK. The effects of a commercial dietary supplement on human performance. *Am J Clin Nutr* 40: 287–293, 2003.
8. Bartoli M and Richard I. Calpains in muscle wasting. *Int J Biochem Cell Biol* 37: 2115–2133, 2005.
9. Bhat HK, Calaf G, Hei TK, Loya T, and Vadgama JV. Critical role of oxidative stress in estrogen-induced carcinogenesis. *Proc Natl Acad Sci USA* 100: 3913–3918, 2003.
10. Block G, Dietrich M, Norkus EP, Morrow JD, Hudes M, Caan B, and Packer L. Factors associated with oxidative stress in human populations. *Am J Epidemiol* 156: 274–285, 2002.
11. Carmeli E, Coleman R, and Reznick AZ. The biochemistry of aging muscle. *Exp Gerontol* 37: 477–489, 2002.
12. Cesari M, Kritchevsky SB, Baumgartner RN, Atkinson HH, Penninx BWJH, Lenchik L, Palla SL, Ambrosius WT, Tracy RP, and Pahor M. Sarcopenia, obesity and inflammation—Results from the TRAIN study. *Am J Clin Nutr* 82: 428–434, 2005.
13. Cesari M, Kritchevsky SB, Nicklas BJ, Penninx BWJH, Holvoet P, Koh-Banerjee P, Cummings S, Harris TB, Newman AB, and Pahor M. Lipoprotein peroxidation and mobility limitation: results from the Health, Aging and Body Composition Study. *Arch Intern Med* 165: 2148–2154, 2005.
14. Cesari M, Pahor M, Bartali B, Cherubini A, Penninx BW, Williams GR, Atkinson H, Martin A, Guralnik JM, and Ferrucci L. Antioxidants and physical performance in elderly persons: the Invecchiare in Chianti (InCHIANTI) study. *Am J Clin Nutr* 79: 289–294, 2004.
15. Cohen HJ, Pieper CF, Harris TB, Rao KM, and Currie MS. The association of plasma IL-6 levels with functional disability in community-dwelling elderly. *J Gerontol A Biol Sci Med Sci* 52: M201–M208, 1997.
16. Davì G, Alessandrini P, Mezzetti A, Minotti G, Bucciarelli T, Costantini F, Cipollone F, Bon GB, Ciabattoni G, and Patrono C. *In vivo* formation of 8-epi-prostaglandin F2 alpha is increased in hypercholesterolemia. *Arterioscler Thromb Vasc Biol* 17: 3230–3235, 1997.
17. Davì G, Basili S, Vieri M, Cipollone F, Santarone S, Alessandri C, Gazzaniga P, Cordova C, Violi F, and the Chronic Obstructive Bronchitis and Haemostasis Study Group. Enhanced thromboxane biosynthesis in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 156: 1794–1799, 1997.
18. Davì G, Chiarelli F, Santilli F, Pomilio M, Vigneri S, Falco A, Basili S, Ciabattoni G, and Patrono C. Enhanced lipid peroxidation and platelet activation in the early phase of type 1 diabetes mellitus—Role of interleukin-6 and disease duration. *Circulation* 107: 3199–3203, 2003.
19. Davì G, Ciabattoni G, Consoli A, Mezzetti A, Falco A, Santarone S, Pennese E, Vitacolonna E, Bucciarelli T, Costantini F, Capani F, and Patrono C. *In vivo* formation of 8-iso-prostaglandin F2 alpha and platelet activation in diabetes mellitus: effects of improved metabolic control and vitamin E supplementation. *Circulation* 99: 224–229, 1999.
20. Davì G, DiMinno G, Coppola A, Andria G, Cerbone AM, Madonna P, Tufano A, Falco A, Marchesani P, Ciabattoni G, and Patrono C. Oxidative stress and platelet activation in homozygous homocystinuria. *Circulation* 104: 1124–1128, 2001.
21. Davì G, Falco A, and Patrono C. Determinants of F2-isoprostane biosynthesis and inhibition in man. *Chem Phys Lipids* 128: 149–163, 2004.
22. Davì G, Guagnano MT, Ciabattoni G, Basili S, Falco A, Marinopiccoli M, Nutini M, Sensi S, and Patrono C. Platelet activation in obese women: role of inflammation and oxidative stress. *JAMA* 288: 2008–2014, 2002.
23. Dietrich M, Block G, Hudes M, Morrow JD, Norkus EP, Traber MG, Cross CE, and Packer L. Antioxidant supplementation decreases lipid peroxidation biomarker F2-

isoprostane in plasma of smokers. *Cancer Epidemiol Biomarkers Prev* 11: 7–13, 2002.
24. Dworski R, Roberts LJ, Murray JJ, Morrow JD, Hartert TV, and Sheller JR. Assessment of oxidant stress in allergic asthma by measurement of the major urinary metabolite of F2-isoprostane, 15-F2t-IsoP (8-iso-PGF2alpha). *Clin Exp Allergy* 31: 387–390, 2001.
25. Eikelboom JW, Hirsh J, Weitz JI, Johnston M, Yi Q, and Yusuf S. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. *Circulation* 105: 1650–1655, 2002.
26. Facchini FS, Hua NW, Reaven GM, and Stoohs RA. Hyperinsulinemia: the missing link among oxidative stress and age-related diseases? *Free Radic Biol Med* 29: 1302–1306, 2000.
27. Fai Poon H, Calabrese V, Scapagnini G, and Butterfield DA. Free radicals: key to brain aging and heme oxygenase as a cellular response to oxidative stress. *J Gerontol A Biol Sci Med Sci* 59A: 478–493, 2004.
28. Fano G, Mecocci P, Vecchiet J, Belia S, Fulle S, Polidori MC, Felzani G, Senin U, Vecchiet L, and Beal MF. Age and sex influence on oxidative damage and functional status in human skeletal muscle. *J Muscle Res Cell Motil* 22: 345–351, 2001.
29. Ferrucci L, Harris TB, Guralnik JM, Tracy RP, Corti MC, Cohen HJ, Penninx BWJH, Pahor M, Wallace RB, and Havlik RJ. Serum IL-6 level and the development of disability in older persons. *J Am Geriatr Soc* 47: 639–646, 1999.
30. Fiebich BL, Hull M, Lieb K, Gyufko K, Berger M, and Bauer J. Prostaglandin E2 induces interleukin-6 synthesis in human astrocytoma cells. *J Neurochem* 68: 704–709, 1997.
31. Frei B, England L, and Ames BN. Ascorbate is an outstanding antioxidant in human blood plasma. *Proc Natl Acad Sci USA* 86: 6377–6381, 1989.
32. Frei B, Forte TM, Ames BN, and Cross CE. Gas phase oxidants of cigarrette smoke induce lipid peroxidation and changes in lipoprotein properties in human blood plasma. *Biochem J* 277: 133–138, 1991.
33. Fried LP and Guralnik JM. Disability in older adults: evidence regarding significance, etiology, and risk. *J Am Geriatr Soc* 45: 92–100, 1997.
34. Fulle S, Protasi F, Di Tano G, Pietrangelo T, Beltramin A, Boncompagni S, Vecchiet L, and Fano G. The contribution of reactive oxygen species to sarcopenia and muscle ageing. *Exp Gerontol* 39: 17–24, 2004.
35. Gale CR, Ashurst HE, Powers HJ, and Martyn CN. Antioxidant vitamin status and carotid atherosclerosis in the elderly. *Am J Clin Nutr* 74: 402–408, 2001.
36. Gaziano JM, Manson JE, Branch LG, Colditz GA, Willett WC, and Buring JE. A prospective study of consumption of carotenoids in fruits and vegetables and decreased cardiovascular mortality in the elderly. *Ann Epidemiol* 5: 255–260, 1995.
37. Goll DE, Thompson VF, Li H, Wei W, and Cong J. The calpain system. *Physiol Rev* 83: 731–801, 2003.
38. Greco A, Minghetti L, and Levi G. Isoprostanes, novel markers of oxidative injury, help understanding the pathogenesis of neurodegenerative diseases. *Neurochem Res* 25: 1357–1364, 2000.
39. Greco A, Minghetti L, Sette G, Fieschi C, and Levi G. Cerebrospinal fluid isoprostane shows oxidative stress in patients with multiple sclerosis. *Neurology* 53: 1876–1879, 1999.
40. Grune T, Merker K, Sandig G, and Davies KJ. Selective degradation of oxidatively modified protein substrates by the proteasome. *Biochem Biophys Res Comm* 305: 709–718, 2003.
41. Halliwell B, and Gutteridge JMC. Role of free radicals and catalytic metal ions in human disease: an overview. *Methods Enzymol* 186: 1–85, 1990.
42. Handelman GJ, Walter MF, Adhikarla R, Gross J, Dallal GE, Levin NW, and Blumberg JB. Elevated plasma F2-isoprostanes in patients on long-term hemodialysis. *Kidney Int* 59: 1960–1966, 2001.
43. Harman D. Aging: a theory based on free radical and radiation chemistry. *J Gerontol* 2: 298–300, 1957.
44. Harman D. The free radical theory of aging. *Antioxid Redox Signal* 5: 557–561, 2003.
45. Haslett P, Hempstead M, Seidman C, Diakun J, Vasquez D, Freedman VH, and Kaplan G. The metabolic and immunologic effects of short-term thalidomide treatment of patients infected with the human immunodeficiency virus. *AIDS Res Hum Retroviruses* 13: 1047–1054, 1997.
46. Hauer K, Hildebrandt W, Sehl Y, Edler L, Oster P, and Dröge W. Improvement in muscular performance and decrease in tumor necrosis factor level in old age after antioxidant treatment. *J Mol Med* 81: 118–125, 2003.
47. Helmersson J, and Basu S. F2-isoprostane excretion rate and diurnal variation in human urine. *Prostaglandins Leukot Essent Fatty Acids* 61: 203–205, 1999.
48. Hishinuma T, Tsukamoto H, Suzuki K, and Mizugaki M. Relationship between thromboxane/prostaclicin ratio and diabetic vascular complications. *Prostaglandins Leukot Essent Fatty Acids* 53: 191–196, 2001.
49. Hoshino E, Pichard C, Greenwood CE, Huo GC, Cameron RG, Kurian R, Kearns JP, Allard JP, and Jeejeebhoy KN. Body composition and metabolic rate in rat during a continuous infusion of cachectin. *Am J Physiol* 260: E27–E36, 1991.
50. Hu P, Reuben DB, Crimmins EM, Harris TB, Huang MH, and Seeman TE. The effects of serum beta-carotene concentration and burden of inflammation on all-cause mortality risk in high-functioning older persons: MacArthur Studies of Successful Aging. *J Gerontol A Biol Sci Med Sci* 59A: 849–854, 2004.
51. Ikonomidis I, Lekakis J, Vamvakou G, Andreotti F, and Nihoyannopoulos P. Cigarette smoking is associated with increased circulating proinflammatory and procoagulant markers in patients with chronic coronary artery disease: effects of aspirin treatment. *Am Heart J* 149: 832–839, 2005.
52. Janssen LJ. Isoprostanes: an overview and putative roles in pulmonary pathophysiology. *Am J Physiol Lung Cell Mol Physiol* 280: L1067–L1082, 2001.
53. Keaney JF, Jr., Larson MG, Vasan RS, Wilson PWF, Lipinska I, Corey D, Massaro JM, Sutherland P, Vita JA, and Benjamin EJ. Obesity and systemic oxidative stress—

Clinical correlates of oxidative stress in The Framingham Study. *Arterioscler Thromb Vasc Biol* 23: 434–439, 2003.
54. Kostikas K, Papatheodorou G, Psathakis K, Panagou P, and Loukides S. Oxidative stress in expired breath condensate of patients with COPD. *Chest* 124: 1373–1380, 2003.
55. Kozawa O, Suzuki A, Tokuda H, and Uematsu T. Prostaglandin F2alpha stimulates interleukin-6 synthesis via activation of PKC in osteoblast-like cells. *Am J Physiol* 272: E208–E211, 1997.
56. Kris-Etherton PM, Lichtenstein AH, Howard BV, Steinberg D, and Witztum JL, for the Nutrition Committee of the American Heart Association Council on Nutrition Physical Activity and Metabolism. Antioxidant vitamin supplements and cardiovascular disease. *Circulation* 110: 637–641, 2004.
57. Kurokawa K, Tanaka H, Tanaka S, and Abe S. Circadian characteristics of urinary leukotriene E4 in healthy subjects and nocturnal asthmatic patients. *Chest* 120: 1822–1828, 2001.
58. Leeuwenburgh C. The role of apoptosis in sarcopenia. *J Gerontol A Biol Sci Med Sci* 58: 999–1001, 2003.
59. Levi M, van der Poll T, and Buller HR. Bidirectional relation between inflammation and coagulation. *Circulation* 109: 2698–2704, 2004.
60. Lim PS, Chang YM, Thien LM, Wang NP, Yang CC, Chen TT, and Hsu WM. 8-iso-prostaglandin F2alpha as a useful clinical biomarker of oxidative stress in ESRD patients. *Blood Purif* 20: 537–542, 2002.
61. Lindemann S, Tolley ND, Dixon DA, McIntyre TM, Prescott SM, Zimmerman GA, and Weyrich AS. Activated platelets mediate inflammatory signaling by regulated interleukin 1 beta synthesis. *J Cell Biol* 154: 485–490, 2001.
62. Liu T, Stern A, Roberts LJ, and Morrow JD. The isoprostanes: novel prostaglandin-like products of the free radical-catalyzed peroxidation of arachidonic acid. *J Biomed Sci* 6: 226–235, 1999.
63. Longini M, Perrone S, Kenanidis A, Vezzosi P, Marzocchi B, Petraglia F, Centini G, and Buonocore G. Isoprostanes in amniotic fluid: a predictive marker for fetal growth restriction in pregnancy. *Free Radic Biol Med* 38: 1537–1541, 2005.
64. Longmire AW, Swift LL, Roberts LJ, Awad JA, Burk RF, and Morrow JD. Effect of oxygen tension on the generation of F2-isoprostanes and malondialdehyde in peroxidizing rat liver microsomes. *Biochem Pharmacol* 47: 1173–1177, 1994.
65. Lynch SM, Morrow JD, Roberts LJ, and Frei B. Formation of non-cyclooxygenase-derived prostanoids (F2-isoprostanes) in plasma and low density lipoprotein exposed to oxidative stress *in vivo. J Clin Invest* 93: 998–1004, 1994.
66. Mallat Z, Philip I, Lebret M, Chatel D, Maclouf J, and Tedgui A. Elevated levels of 8-iso-prostaglandin F2alpha in pericardial fluid of patients with heart failure: a potential role for *in vivo* oxidant stress in ventricular dilatation and progression to heart failure. *Circulation* 97: 1536–1539, 1998.
67. Maxwell SRJ. Prospects for the use of antioxidant therapies. *Drugs* 49: 345–361, 1995.
68. McConnell JP, Cheryk LA, Durocher A, Bruno A, Bang NU, Fleck JD, Williams L, Biller J, and Meschia JF. Urinary 11-dehydro-thromboxane B2 and coagulation markers measured within 24 h of human acute ischemic stroke. *Neurosci Lett* 313: 88–92, 2001.
69. Meade EA, McIntyre TM, Zimmerman GA, and Prescott SM. Peroxisome proliferators enhance cyclooxygenase-2 expression in epithelial cells. *J Biol Chem* 274: 8328–8334, 1999.
70. Mecocci P, Fano G, Fulle S, MacGarvey U, Shinobu L, Polidori MC, Cherubini A, Vecchiet J, Senin U, and Beal MF. Age-dependent increases in oxidative damage to DNA, lipids, and proteins in human skeletal muscle. *Free Radic Biol Med* 26: 303–308, 1999.
71. Messier SP, Loeser RF, Miller GD, Morgan TM, Rejeski WJ, Sevick MA, Ettinger WH Jr, Pahor M, and Williamson JD. Exercise and diet weight loss in overweigh and obese older adults with knee osteoarthritis—The Arthritis, Diet, and Activity Promotion Trial. *Arthritis Rheum* 50: 1501–1510, 2004.
72. Minuz P, Patrignani P, Gaino S, Degan M, Menapace L, Tommasoli R, Seta F, Capone ML, Tacconelli S, Palatresi S, Bencini C, Del Vecchio C, Mansueto G, Arosio E, Santonastaso CL, Lechi A, Morganti A, and Patrono C. Increased oxidative stress and platelet activation in patients with hypertension and renovascular disease. *Circulation* 106: 2800–2805, 2002.
73. Minuz P, Patrignani P, Gaino S, Seta F, Capone ML, Tacconelli S, Degan M, Faccini G, Fornasiero A, Talamini G, Tommasoli R, Arosio E, Lechi Santonastaso C, Lechi A, and Patrono C. Determinants of platelet activation in human essential hypertension. *Hypertension* 43: 64–70, 2004.
74. Montuschi P, Ciabattoni G, Paredi P, Pantelidis P, duBois RM, Kharitonov SA, and Barnes PJ. 8-Isoprostane as a biomarker of oxidative stress in interstitial lung diseases. *Am J Respir Crit Care Med* 158: 1524–1527, 1998.
75. Moore KP, Darley-Usmar V, Morrow J, and Roberts LJ, II. Formation of F2-isoprostanes during oxidation of human low-density lipoprotein and plasma by peroxynitrite. *Circ Res* 77: 335–341, 1995.
76. Morley JE, Baumgartner RN, Roubenoff R, Mayer J, and Nair KS. Sarcopenia. *J Lab Clin Med* 137: 231–243, 2001.
77. Morrow JD. Quatification of isoprostanes as indices of oxidant stress and the risk of atherosclerosis in humans. *Arterioscler Thromb Vasc Biol* 25: 1–8, 2005.
78. Morrow JD, Frei B, Longmire AW, Gaziano JM, Lynch SM, Shyr Y, Strauss WE, Oates J, and Roberts LJ. Increase in circulating products of lipid peroxidation (F2-isoprostanes) in smokers: smoking as a cause of oxidative damage. *N Engl J Med* 332: 1198–1203, 1995.
79. Morrow JD, Hill KE, Burk RF, Nammour TM, Badr KF, and Roberts LJ, II. A series of prostaglandin F2-like compounds are produced *in vivo* in humans by a non-cyclooxygenase free radical-catalized mechanism. *Proc Natl Acad Sci USA* 87: 9383–9387, 1990.
80. Morrow JD, Minton TA, and Roberts LJ, II. The F2-isoprostane, 8-epi-prostaglandin F2 alpha, a potent agonist of the vascular thromboxane/endoperoxide receptor, is a thromboxane/endoperoxide receptor antagonist. *Prostaglandins* 44: 155–163, 1992.
81. Morrow JD, Oates JA, Roberts LJ, II, Zackert WE, Mitchell TA, Lazarus G, and Guzzo C. Increased forma-

tion of thromboxane *in vivo* in humans with mastocytosis. *J Invest Dermatol* 113: 93–97, 1999.
82. Morrow JD and Roberts LJ. The isoprostanes: unique bioactive products of lipid peroxidation. *Prog Lipid Res* 36: 1–21, 1997.
83. Murohara T, Ikeda H, Katoh A, Takajo Y, Otsuka Y, Haramaki N, and Imaizumi T. Vitamin E inhibits lysophosphatidylcholine-induced endothelial dysfunction and platelet activation. *Antioxid Redox Signal* 4: 791–798, 2002.
84. Natarajan R, Lanting L, Gonzales N, and Nadler J. Formation of F2-isoprostanes in vascular smooth muscle cells by elevated glucose and growth factors. *Am J Physiol* 271: H159–H165, 1996.
85. Newman AB, Arnold AM, Naydeck BL, Fried LP, Burke GL, Enright P, Gottdiener J, Hirsch C, O'Leary D, Tracy R, and Cardiovascular Health Study Research Group. "Successful aging": effect of subclinical cardiovascular disease. *Arch Intern Med* 163: 2315–2322, 2003.
86. Niki E, Noguchi N, Tsuchihashi H, and Gotoh N. Interaction among vitamin C, vitamin E, and beta-carotene. *Am J Clin Nutr* 62: 1322S–1326S, 1995.
87. Odding E, Valkenburg HA, Stam HJ, and Hofman A. Determinants of locomotor disability in people aged 55 years and over: the Rotterdam Study. *Eur J Epidemiol* 17: 1033–1041, 2001.
88. Oostenbrug GS, Mensink RP, Hardeman MR, De Vries T, Brouns F, and Hornstra G. Exercise performance, red blood cell deformability, and lipid peroxidation: effects of fish oil and vitamin E. *J Appl Physiol* 83: 746–752, 1997.
89. Owen RW. Biomarkers in colorectal cancer. *IARC Sci Publ* 154: 101–111, 2001.
90. Pansarasa O, Castagna L, Colombi B, Vecchiet J, Felzani G, and Marzatico F. Age and sex differences in human skeletal muscle: role of reactive oxygen species. *Free Radic Res* 33: 287–293, 2000.
91. Pasceri V, Willerson JT, and Yeh ETH. Direct proinflammatory effect of C-reactive protein on human endothelial cells. *Circulation* 102: 2165–2168, 2000.
92. Patrignani P, Panara MR, Tacconelli S, Seta F, Bucciarelli T, Ciabattoni G, Alessandrini P, Mezzetti A, Santini G, Sciulli MG, Cipollone F, Davì G, Gallina P, Bittolo Bon G, and Patrono C. Effects of vitamin E supplementation on F2-isoprostane and thromboxane biosynthesis in healthy cigarette smokers. *Circulation* 102: 539–545, 2000.
93. Patrono C, Ciabattoni G, and Davì G. Thromboxane biosynthesis in cardiovascular diseases. *Stroke* 21: IV130–IV133, 1990.
94. Patrono C, Falco A, and Davì G. Isoprostane formation and inhibition in atherothrombosis. *Curr Opin Pharmacol* 5: 198–203, 2005.
95. Phillips T and Leeuwenburgh C. Lifelong aspirin supplementation as a means to extending life span. *Rejuvenation Res* 7: 243–251, 2004.
96. Pignatelli P, Pulcinelli FM, Lenti L, Gazzaniga PP, and Violi F. Vitamin E inhibits collagen-induced platelet activation by blunting hydrogen peroxide. *Arterioscler Thromb Vasc Biol* 19: 2542–2547, 1999.
97. Powers SK, Kavazis AN, and DeRuisseau KC. Mechanisms of disuses muscle atrophy: role of oxidative stress. *Am J Physiol Regul Integr Comp Physiol* 288: 337–344, 2005.
98. Pratico D and Fitzgerald GA. Generation of 8-epi-prostaglandin F2alpha by human monocytes. Discriminate production by reactive oxygen species and prostaglandin endoperoxide synthase-2. *J Biol Chem* 271: 8919–8924, 1996.
99. Pratico D, Smyth EM, Violi F, and FitzGerald GA. Local amplification of platelet function by 8-epi prostaglandin F2 alpha is not mediated by thromboxane receptor isoforms. *J Biol Chem* 271: 14916–14924, 1996.
100. Pratico D, Tangirala RK, Rader DJ, Rokach J, and Fitzgerald GA. Vitamin E suppresses isoprostane generation in vivo and reduces atherosclerosis in ApoE-deficient mice. *Nat Med* 4: 1189–1192, 1998.
101. Prince MR, LaMuraglia GM, and MacNichol EF. Increased preferential absorption in human atherosclerotic plaque with oral beta-carotene: implications for laser endarterectomy. *Circulation* 78: 338–344, 1988.
102. Reilly M, Delanty N, Lawson JA, and Fitzgerald GA. Modulation of oxidant stress *in vivo* in chronic cigarette smokers. *Circulation* 94: 19–25, 1996.
103. Richter C. Biophysical consequences of lipid peroxidation in membranes. *Chem Phys Lipids* 44: 175–189, 1987.
104. Sampson MJ, Gopaul N, Davies IR, Hughes DA, and Carrier MJ. Plasma F2 isoprostanes: direct evidence of increased free radical damage during acute hyperglycemia in type 2 diabetes. *Diabetes Care* 25: 537–541, 2002.
105. Sanchez-Moreno C, Dashe JF, Scott T, Thaler D, Folstein MF, and Martin A. Decreased levels of plasma vitamin C and increased concentrations of inflammatory and oxdiative stress markers after stroke. *Stroke* 35: 163–168, 2004.
106. Sciulli MG, Filabozzi P, Tacconelli S, Padovano R, Ricciotti E, Capone ML, Grana M, Carnevale V, and Patrignani P. Platelet activation in patients with colorectal cancer. *Prostaglandins Leukot Essent Fatty Acids* 72: 79–83, 2005.
107. Semba RD, Blaum C, Guralnik JM, Moncrief DT, Ricks Mo, and Fried LP. Carotenoid and vitamin E status are associated with indicators of sarcopenia among older women living in the community. *Aging Clin Exp Res* 15: 482–487, 2003.
108. Shi X, Ding M, Dong Z, Chen F, Ye J, Wang S, Leonard SS, Castranova V, and Vallyathan V. Antioxidant properties of aspirin: characterization of the ability of aspirin to inhibit silica-induced lipid peroxidation, DNA damage, NF-kappaB activation, and TNF-alpha production. *Mol Cell Biochem* 199: 93–102, 1999.
109. Siems W, Capuozzo E, Lucano A, Salerno C, and Crifo C. High sensitivity of plasma membrane ion transport ATPases from human neutrophils towards 4-hydroxy-2,3-trans-nonenal. *Life Sci* 73: 2583–2590, 2003.
110. Spittle MA, Hoenich NA, Handelman GJ, Adhikarla R, Homel P, and Levin NW. Oxidative stress and inflammation in hemodialysis patients. *Am J Kidney Dis* 38: 1408–1413, 2001.
111. Squier TC and Bigelow DJ. Protein oxidation and age-dependent alterations in calcium homeostasis. *Front Biosci* 5: D504–D526, 2000.
112. Steinberg D. Oxidative modification of LDL and atherogenesis. *Circulation* 95: 1062–1071, 1997.

113. Stuck AE, Walthert JM, Nikolaus T, Bula CJ, Hohmann C, and Beck JC. Risk factors for functional status decline in community-living elderly people: a systematic literature review. *Soc Sci Med* 48: 445–469, 1999.
114. Upritchard JE, Schuurman CRWC, Wiersma A, Tijburg LBM, Coolen SAJ, Rijken PJ, and Wiseman SA. Spread supplemented with moderate doses of vitamin E and carotenoids reduces lipid peroxidation in healthy, nonsmoking adults. *Am J Clin Nutr* 78: 985–992, 2003.
115. Volpato S, Blaum C, Resnick H, Ferrucci L, Fried LP, Guralnik JM, and Women's Health and Aging Study. Comorbidities and impairments explaining the association between diabetes and lower extremity disability: The Women's Health and Aging Study. *Diabetes Care* 25: 678–683, 2002.
116. Volpato S, Guralnik JM, Ferrucci L, Balfour J, Chaves P, Fried LP, and Harris TB. Cardiovascular disease, interleukin-6, and risk of mortality in older women—The Women's Health and Aging Study. *Circulation* 103: 947–953, 2001.
117. Ward WF, Qi W, Van Remmen H, Zackert WE, Roberts LJ, II, and Richardson A. Effects of age and caloric restriction on lipid peroxidation: measurement of oxidative stress by F2-isoprostane levels. *J Gerontol A Biol Sci Med Sci* 60A: 847–851, 2005.
118. Wijnen MHWA, Coolen SAJ, Vader HL, Reijenga JC, Huf FA, and Roumen RMH. Antioxidants reduce oxidative stress in claudicants. *J Surg Res* 96: 183–187, 2001.
119. Witztum JL. The oxidation hypothesis of atherosclerosis. *Lancet* 344: 793–795, 1994.
120. Yudkin JS, Kumari M, Humphries SE, and Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? *Atherosclerosis* 148: 209–214, 2000.

Address reprint requests to:
Matteo Cesari, M.D., Ph.D.
Department of Aging and Geriatric Research
College of Medicine, Institute on Aging
University of Florida
1329 SW 16th Street, Room 5372
Gainesville, FL 32608

E-mail: mcesari@aging.ufl.edu

Received after final revision September 22, 2005; accepted October 3, 2005.

This article has been cited by:

1. Todd M. Manini, David W. Russ, Brian C. ClarkThe Complex Relation between Muscle Mass and Muscle Strength 74-103. [CrossRef]
2. Heather K. Vincent, Sara N. Raiser, Kevin R. Vincent. 2012. The aging musculoskeletal system and obesity-related considerations with exercise. *Ageing Research Reviews* **11**:3, 361-373. [CrossRef]
3. Barbara Tomasello , Salvatore Grasso , Giuseppe Malfa , Stefania Stella , Marco Favetta , Marcella Renis . 2012. Double-Face Activity of Resveratrol in Voluntary Runners: Assessment of DNA Damage by Comet Assay. *Journal of Medicinal Food* **15**:5, 441-447. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
4. M. Cesari, S. B. Kritchevsky, B. Nicklas, A. M. Kanaya, P. Patrignani, S. Tacconelli, G. J. Tranah, G. Tognoni, T. B. Harris, R. A. Incalzi, A. B. Newman, M. Pahor. 2012. Oxidative Damage, Platelet Activation, and Inflammation to Predict Mobility Disability and Mortality in Older Persons: Results From the Health Aging and Body Composition Study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* . [CrossRef]
5. David Gonzalo-Calvo, Benjamín Fernández-García, Beatriz Luxán-Delgado, Susana Rodríguez-González, Marina García-Macia, Francisco Manuel Suárez, Juan José Solano, María Josefa Rodríguez-Colunga, Ana Coto-Montes. 2012. Chronic training increases blood oxidative damage but promotes health in elderly men. *AGE* . [CrossRef]
6. M. Pahor, Matteo Cesari. 2011. Designing phase II B trials in Sarcopenia: The best target population. *The journal of nutrition, health & aging* . [CrossRef]
7. Matteo Cesari, Marco Pahor, Raffaele Antonelli Incalzi. 2010. REVIEW: Plasminogen Activator Inhibitor-1 (PAI-1): A Key Factor Linking Fibrinolysis and Age-Related Subclinical and Clinical Conditions. *Cardiovascular Therapeutics* **28**:5, e72-e91. [CrossRef]
8. Hae Young Chung, Matteo Cesari, Stephen Anton, Emanuele Marzetti, Silvia Giovannini, Arnold Young Seo, Christy Carter, Byung Pal Yu, Christiaan Leeuwenburgh. 2009. Molecular inflammation: Underpinnings of aging and age-related diseases. *Ageing Research Reviews* **8**:1, 18-30. [CrossRef]
9. D MARI, R COPPOLA, R PROVENZANO. 2008. Hemostasis factors and aging. *Experimental Gerontology* **43**:2, 66-73. [CrossRef]
10. Christiaan Leeuwenburgh , Tomas A. Prolla . 2006. Genetics, Redox Signaling, Oxidative Stress, and Apoptosis in Mammalian Aging. *Antioxidants & Redox Signaling* **8**:3-4, 503-505. [Citation] [Full Text PDF] [Full Text PDF with Links]