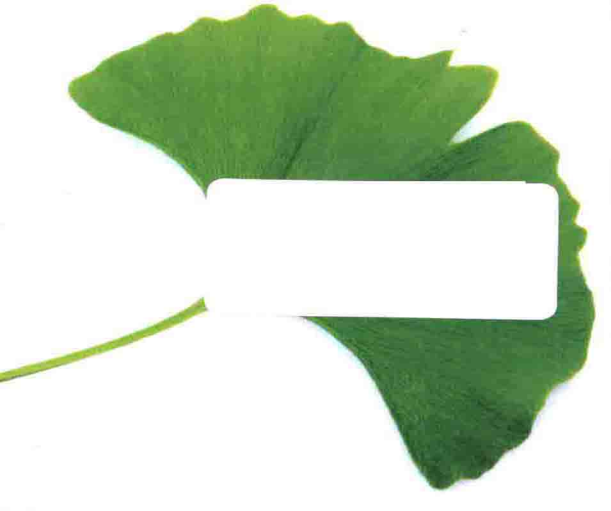

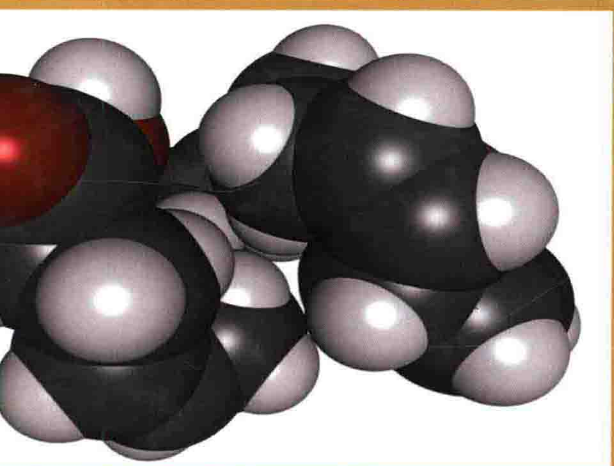


AGING

Oxidative Stress and Dietary Antioxidants

Edited by
VICTOR R. PREEDY

AGING: OXIDATIVE STRESS AND DIETARY ANTIOXIDANTS

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King's College London, London, UK

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Preface

In the past few decades there have been major advances in our understanding of the etiology of disease and its causative mechanisms. Increasingly it is becoming evident that free radicals are contributory agents: either to initiate or propagate the pathology or add to an overall imbalance. Furthermore, reduced dietary antioxidants can also lead to specific diseases and preclinical organ dysfunction. On the other hand, there is abundant evidence that dietary and other naturally occurring antioxidants can be used to prevent, ameliorate or impede such diseases. The science of oxidative stress and free radical biology is rapidly advancing and new approaches include the examination of polymorphism and molecular biology. The more traditional sciences associated with organ functionality continue to be explored but their practical or translational applications are now more sophisticated.

However, most textbooks on dietary antioxidants do not have material on the fundamental biology of free radicals, especially their molecular and cellular effects on pathology. They may also fail to include material on the nutrients and foods which contain antioxidative activity. In contrast, most books on free radicals and organs disease have little or no text on the usage of natural antioxidants.

The series **Oxidative Stress and Dietary Antioxidants** aims to address the aforementioned deficiencies in the knowledge base by combining in a single volume the science of oxidative stress and the putative therapeutic usage of natural antioxidants in the diet, its food matrix or plants. This is done in relation to a single organ, disease or pathology. These include cancer, addictions, immunology, HIV, aging, cognition, endocrinology, pregnancy and fetal growth, obesity, exercise, liver, kidney, lungs, reproductive organs, gastrointestinal tract, oral health, muscle, bone, heart, kidney and the CNS.

In the present volume, **Aging: Oxidative Stress and Dietary Antioxidants,** holistic information is imparted within the structured format of two main sections:

1. **Oxidative Stress and Aging**
2. **Antioxidants and Aging**

The first section on **Oxidative Stress and Aging** covers the basic biology of oxidative stress, from molecular biology to physiological pathology. Topics include markers of frailty, skin aging, cardiovascular disease, the liver, arthritis and diabetes. The second section, **Antioxidants and Aging,** covers cellular and molecular processes of vegetarian diets, enteral nutrition, natural antioxidants in foods and the diet, herbs and spices, coenzyme Q10, vitamins C and D, S-equol, zinc, magnesium, tryptophan, melatonin-enriched foods and lycopene. There is also material on the aging processes, age-related pathologies and organ systems, including menopause, physical performance, skin, bone and osteoporosis, the brain and neurodegeneration, the cardiovascular system, diabetes, muscle, arthritis, inflammation, mitochondria and leukocytes. The aforementioned provide a detailed framework for understanding the relationships between aging, oxidative stress and dietary components. However, more scientifically vigorous trials and investigations are needed to determine the comprehensive properties of many of these antioxidants, food items or extracts, as well as any adverse properties they may have.

The series is designed for dietitians and nutritionists, and food scientists, as well as health care workers and research scientists. Contributions are from leading national and international experts including those from world-renowned institutions.

Professor Victor R. Preedy,
King's College London

Contents

8. Antioxidants, Vegetarian Diets and Aging

S. WACHTEL-GALOR, P.M. SIU, I.F.F. BENZIE

9. Enteral Nutrition to Increase Antioxidant Defenses in Elderly Patients

JOSÉ EDUARDO DE AGUILAR-NASCIMENTO

10. Herbs and Spices in Aging

SUHAILA MOHAMED

11. Coenzyme Q_{10} as an Antioxidant in the Elderly

ELENA M. YUBERO-SERRANO, ANTONIO GARCIA-RIOS, JAVIER DELGADO-LISTA, PABLO PÉREZ-MARTINEZ, ANTONIO CAMARGO, FRANCISCO PEREZ-JIMENEZ, JOSE LOPEZ-MIRANDA

12. Vitamin C and Physical Performance in the Elderly

KYOKO SAITO, ERIKA HOSOI, AKIHITO ISHIGAMI, TETSUJI YOKOYAMA

13. Tryptophan and Melatonin-Enriched Foodstuffs to Improve Antioxidant Status in Aging

M. GARRIDO, A.B. RODRÍGUEZ, M.P. TERRÓN

14. Protective Effects of Vitamin C on Age-Related Bone and Skin Phenotypes Caused by Intracellular Reactive Oxygen Species

SHUICHI SHIBUYA, HIDETOSHI NOJIRI, DAICHI MORIKAWA, HIROFUMI KOYAMA, TAKAHIKO SHIMIZU

15. S-Equol, an Antioxidant Metabolite of Soy Daidzein, and Oxidative Stress in Aging: A Focus on Skin and on the Cardiovascular System

RICHARD L. JACKSON, JEFFREY S. GREIWE, RICHARD J. SCHWEN

24. Lycopene and Other Antioxidants in the Prevention and Treatment of Osteoporosis in Postmenopausal Women

L.G. RAO, N.N. KANG, A.V. RAO

25. Zinc, Oxidative Stress in the Elderly and Implications for Inflammation

ANANDA S. PRASAD

26. Antioxidant Supplementation in the Elderly and Leukocytes

DAVID SIMAR, CORINNE CAILLAUD

27. Metabolic Mobilization Strategies to Enhance the Use of Plant-Based Dietary Antioxidants for the Management of Type 2 Diabetes

DIPAYAN SARKAR, KALIDAS SHETTY

SECTION 1

OXIDATIVE STRESS AND AGING

CHAPTER

1

Oxidative Stress and Frailty: A Closer Look at the Origin of a Human Aging Phenotype

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List of Abbreviations

ATM ataxia-telangiectasia mutated
ATR ataxia telangiectasia and Rad3-related
BER base excision repair
BubR1 mitotic checkpoint serine/threonine-protein kinase BUB1 beta
CDC25 cell-division cycle 25
CHK1 checkpoint kinase 1
CHK2 checkpoint kinase 2
CREBH cyclic AMP response element binding protein hepatocyte
CuZnSOD copper/zinc superoxide dismutase (SOD1)
DDR DNA-damage response
DHEA dehydroepiandrosterone
DHEAS dehydroepiandrosterone sulfate
eNOS endothelial nitric oxide synthase
ER endoplasmic reticulum
IκB inhibitor of kappa B
IKK1 inhibitor of nuclear factor kappa-B kinase subunit alpha
IKK2 inhibitor of nuclear factor kappa-B kinase subunit beta
IL-2 interleukin-2
IL-6 interleukin-6
IL-8 interleukin-8
IRS-1 insulin receptor substrate-1
JNK kinases c-jun N-terminal kinases
MDA malondialdehyde
MnSOD Mn-superoxide dismutase (SOD2)
MPT mitochondrial permeability transition
mtDNA mitochondrialDNA
MTH1 mutT human homolog 1
NADPH reduced form of nicotinamide adenine dinucleotide phosphate
NER nucleotide excision repair
NF-κB nuclear factor-κB
nNOS neuronal nitric oxide synthase
NUDT5 Nudix (nucleoside diphosphate linked moiety X)-type motif 5
8-OHdG 8-hydroxy-2′-deoxyguanosine
ROS reactive oxygen species
TNF-α tumor necrosis factor-α
WRN Werner protein

INTRODUCTION

Oxidative stress, defined as a disturbance in the prooxidant-antioxidant balance leading to oxidative damage,[1] has a key role in aging. More importantly, an increasing amount of evidence suggests that oxidative stress acts causally in the pathogenesis of numerous age-dependent and age-related chronic diseases. Over the past few decades, frailty has been increasingly recognized as a major health problem for older adults. As a distinct pathologic state, frailty contributes to numerous poor health outcomes independently of diseases and disability, and it is characterized by clinical presentations which are well defined and easily identifiable. Because of years of research, we have a better understanding of the system-level pathogenesis of frailty. It is becoming clear that frailty may have its origin in the fundamental aging process. Oxidative stress could play a crucial role in the cellular-level pathogenesis of frailty. In this chapter, the relationship between oxidative stress and frailty is delineated. To address this issue comprehensively, we attempt to integrate the results from human studies and model organism experiments. After a brief overview of oxidative stress in aging, the better known system-level abnormalities associated with the frailty syndrome are introduced. We then discuss whether and how oxidative stress at cellular levels causes frailty. Finally, we present a model of frailty pathogenesis incorporating the current understanding of frailty at the levels of molecules, cells, organs, and systems.

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OXIDATIVE STRESS AND AGING

Aging represents 'progressive deterioration during the adult period of life that underlies an increasing vulnerability to challenges and a decreasing ability of an organism to survive'.[2] The deterioration is due to progressive accumulation of unrepaired damage and has the following core features: intrinsicality, universality, progressiveness and irreversibility, and it is genetically programmed.[2] The literature suggests that oxidative stress is the major cause of somatic damage.[2] Denham Harman proposed the free-radical theory of aging in 1956, which states that aging results from random deleterious damage to tissue by free radicals. His theory is among the most acknowledged theories of aging.[3] Since then, an increasing amount of evidence has indicated that oxidative stress increases with age and contributes to numerous age-related pathologic processes.[4]

The laboratory model organism experiments provide direct evidence that supports the importance of oxidative stress in aging. Numerous mutations that extend the lifespan of yeast, worms, flies, and mice have elevated antioxidant defenses and reduced oxidative stress. In yeast, major mutations that extend replicative and/or chronologic lifespans involve Ras-AC-PKA or Tor-Sch9 signaling.[5] Lifespan extension associated with altered activities in these pathways has been shown to require the antioxidant enzyme superoxide dismutase (Mn-SOD), which scavenges superoxide free radicals.[5] In *Caenorhabditis elegans*, lifespan extension can be achieved by reducing the activities of insulin/IGF-like signaling pathways (e.g. *age-1* and *daf-2* mutants), thereby activating the Forkhead FoxO transcription factor *daf-16*.[6] Active DAF-16 promotes the transcription of major antioxidant genes, including genes encoding catalases, MnSOD, and CuZnSOD. These antioxidants are necessary for lifespan extension in these mutant worms.[6] As in yeast and worms, insulin/IGF1 signaling pathways affect longevity in mice. Acting downstream of IGF receptors, $p66^{Shc}$ enhances production of mitochondrial reactive oxygen species (ROS) by catalyzing redox reactions, which yield hydrogen peroxide.[7] Deleting $p66^{Shc}$ in mice results in decreased oxidative stress, which correlates with an increased lifespan.[7]

Results of human studies are congruent with the findings of model organism experiments. An age-related increase in oxidative damage to macromolecules has been observed in humans.[8] DNA variants in the genes that modulate oxidative stress were linked to longevity.[9,10]

FRAILTY

Definition

As an extreme phenotype of human aging, frailty is a state of increased vulnerability with a decreased ability to maintain homeostasis.[11] Although it can be compounded by disease or disability, this vulnerability is primarily age related and is caused by a reduced reserve capacity of interconnected physiologic systems that adapt to stressors, leading to a breakdown of homeostasis.[11] Despite the lack of a clear consensus, there are several operational definitions of frailty in the literature; these definitions are based on different theories on the underlying causes of frailty. Comprehensive reviews of the definition of frailty are beyond the scope of this article and can be found elsewhere.[11] Two commonly used definitions are discussed.

According to the operational definition of *frailty phenotype* proposed by Fried et al, a person is considered frail if three or more of the following five criteria are present: unintentional weight loss, muscle weakness, slow walking speed, low physical activity, and exhaustion (Table 1.1).[12] Older adults with one or two of the criteria are considered prefrail, whereas those without any criteria are considered robust.[12] Being the commonly cited operational definition in frailty research, the frailty phenotype is based on the assumption that frailty arises

TABLE 1.1 Frailty Phenotype According to Fried et al[12] [a]

Criteria	Frailty Characteristic	Measure
1	Weight loss (unintentional)	>10 lbs lost unintentionally in prior year (reported)
	Shrinking	
	Sarcopenia	
2	Muscle weakness	Grip strength below cutoff value,[12] adjusted for gender and body mass index
3	Exhaustion Poor endurance	Answering 'moderate or most of the time' to 'I feel that everything I do is an effort' or 'I cannot get going'.
4	Slow walking speed	Walking speed below cutoff value,[12] based on time to walk 15 feet, adjusting for gender and standing height.
5	Low physical activity	Kilocalories expended per week below cutoff value (383 kcal/wk in men; 270 kcal/wk in women)[12]

[a] *An individual is considered frail if three or more of the five criteria are present. People with one or two of the criteria are considered prefrail, whereas those without any criteria are considered robust.*

from unique pathologic processes that are independent of diseases and disability. Previous research has shown that the frailty phenotype is able to predict adverse health outcomes independently of disease and disability, and frail older adults are at greater risk compared with prefrail adults.[12] Moreover, there are clues that specific pathophysiologic processes lead to the development of frailty in the absence of disease.[13]

Unlike the Fried definition, Rockwood et al hypothesized that frailty arises from the accumulation of potentially unrelated diseases, subclinical dysfunctions, and disability, and represents an intermediary mechanism linking these conditions to poor health outcomes.[14] The concept of frailty being a distinct pathologic state, separate from diseases and disability, is less emphasized. Frailty is defined by a frailty index, which is created by counting the number of health deficits in an older adult. The health deficits can be any clinical symptom, sign, disease, disability, laboratory, imaging, or other examination abnormality.[14] Using this definition, frailty is associated with poor health outcomes in different populations.[15]

Clinical Significance

The prevalence of frailty is high. It is estimated that a minimum of 10–25% of people aged 65 years and older (and 30–45% of those aged 85 years and older) are frail.[12] Frailty is the core issue in healthy aging and geriatric medicine. In contrast to the younger population, the older population is characterized by a greater variation in health status, outcomes, or response to therapy, which cannot be explained by age and disease alone.[16] As a measure of biologic age, frailty permits superior risk prediction in older adults compared with chronologic age and diseases. Regardless of the operational definitions used, it has been repeatedly demonstrated that, compared with age and chronic diseases, frailty stratification is more strongly associated with an older adult's risk of poor outcomes, including infections, disabilities, institutionalization, and death.[12,15]

Organ and System Abnormalities Associated with Frailty

As described, frailty is caused by abnormal interconnected physiologic systems, which are essential for maintaining homeostasis. The key physiologic systems currently known to be involved in frailty pathogenesis include the musculoskeletal system (skeletal muscle), metabolism (adiposity, insulin activity), immune system (inflammation), endocrine system (insulin-like growth factor-1, dehydroepiandrosterone sulfate, and testosterone), and autonomic nervous system (Fig. 1.1).[11]

Sarcopenia

Body composition changes with age. An age-related loss of skeletal muscle mass is termed sarcopenia.[17]

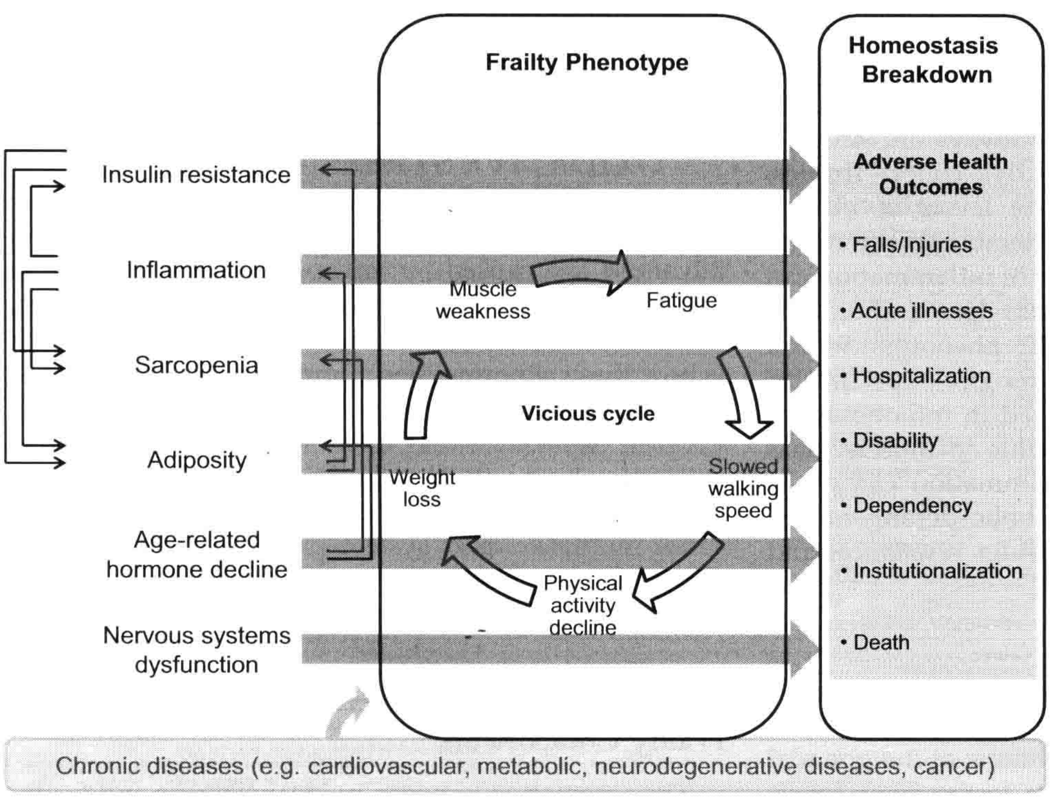

FIGURE 1.1 Organ and system abnormalities associated with frailty. As a human aging phenotype, frailty is characterized by an increased likelihood of homeostasis breakdown. Frailty, either alone or in the presence of diseases, predicts future adverse health outcomes in older adults. Previous research has suggested that several organ/system abnormalities are responsible for homeostasis breakdown at an advanced age, and frailty may represent the clinical manifestations of the pathogenic processes. The key pathogenic processes are (i) insulin resistance; (ii) inflammation; (iii) sarcopenia; (iv) adiposity; (v) age-related hormone decline; and (vi) nervous system dysfunction.[11] These processes are interrelated, and a vicious cycle typically develops. Subclinical diseases may have a role in frailty development.[16]