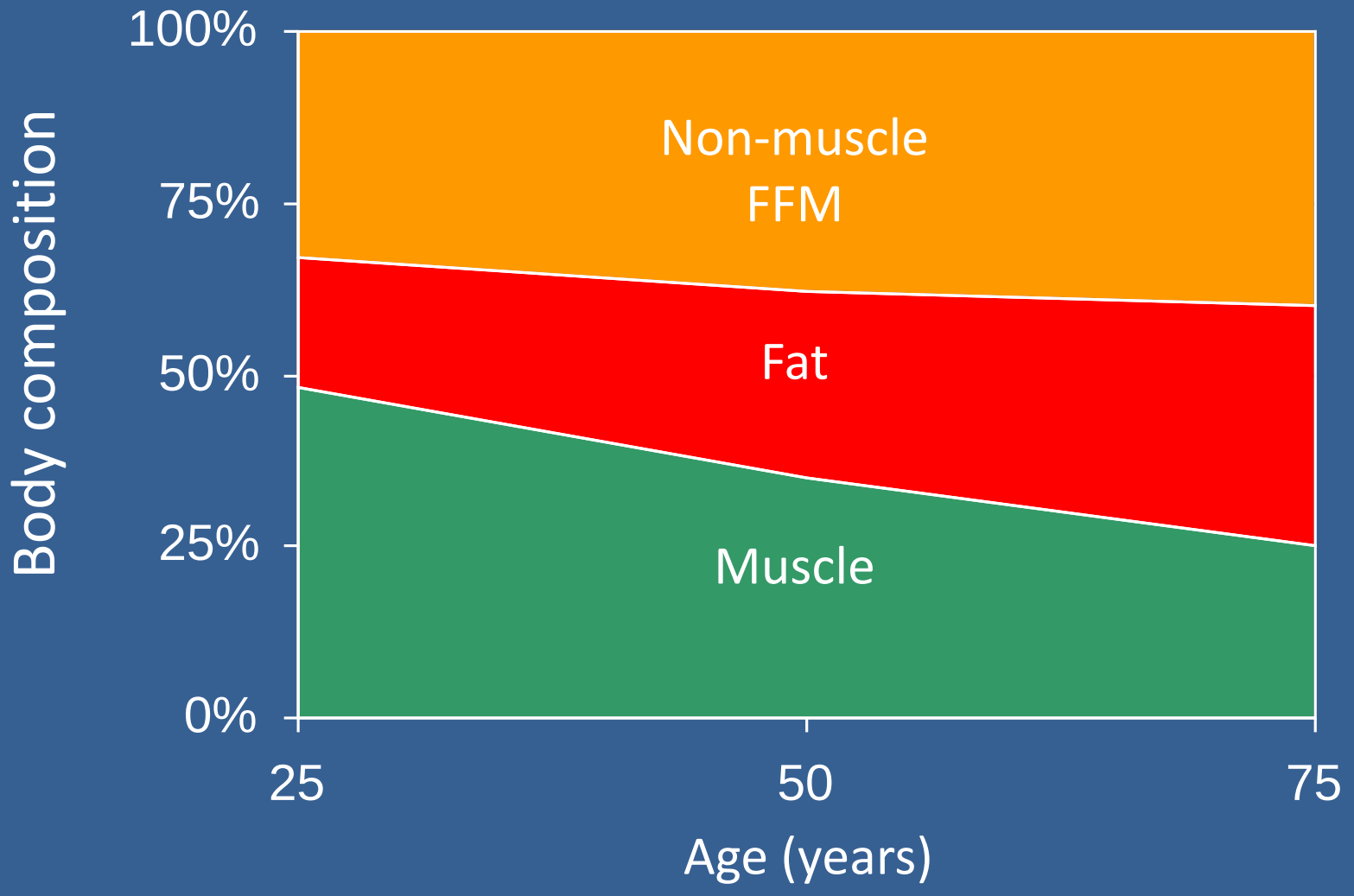
Oxidative stress, antioxidant intervention and sarcopenia

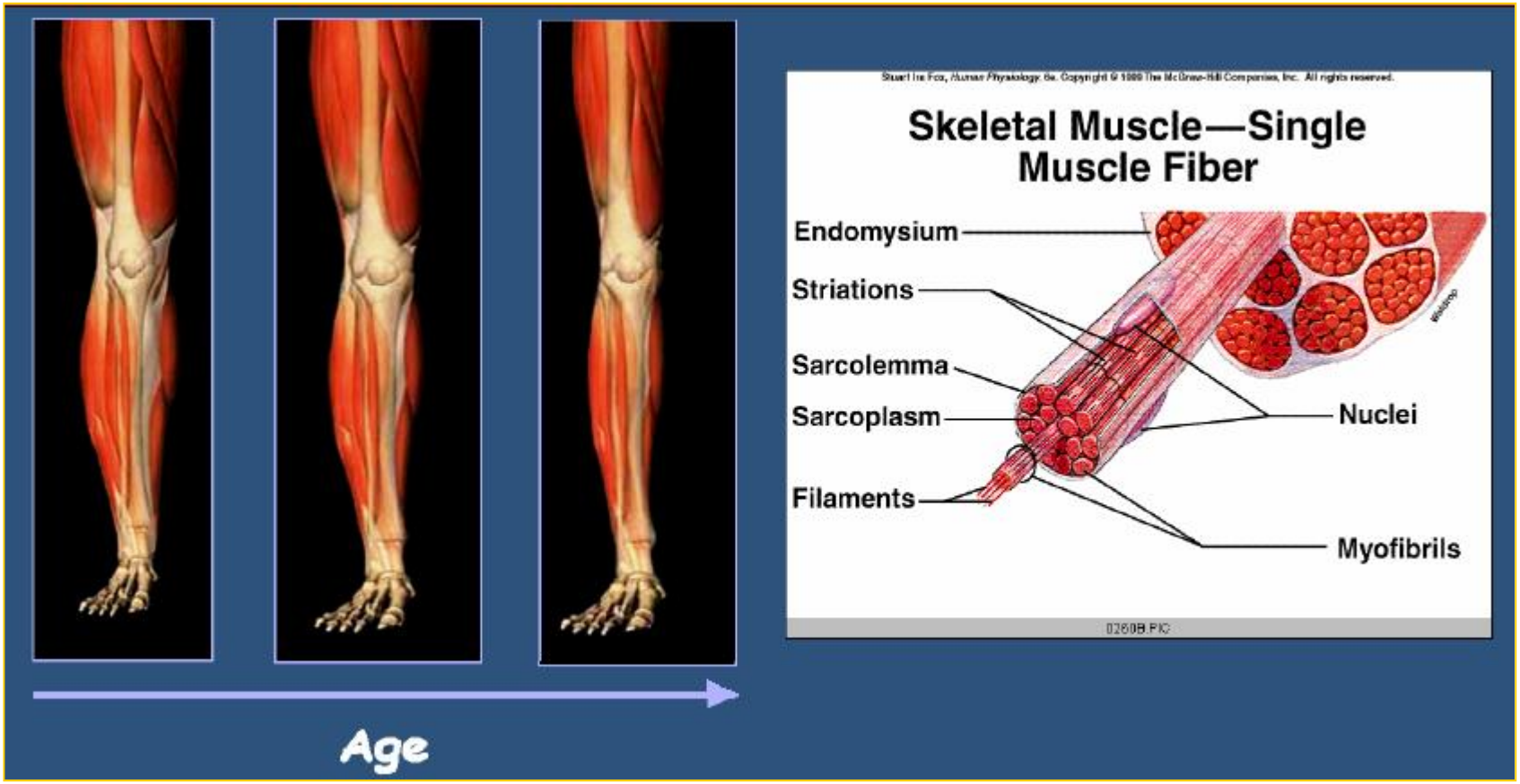
Francesco Marotta, MD, PhD (Japan)

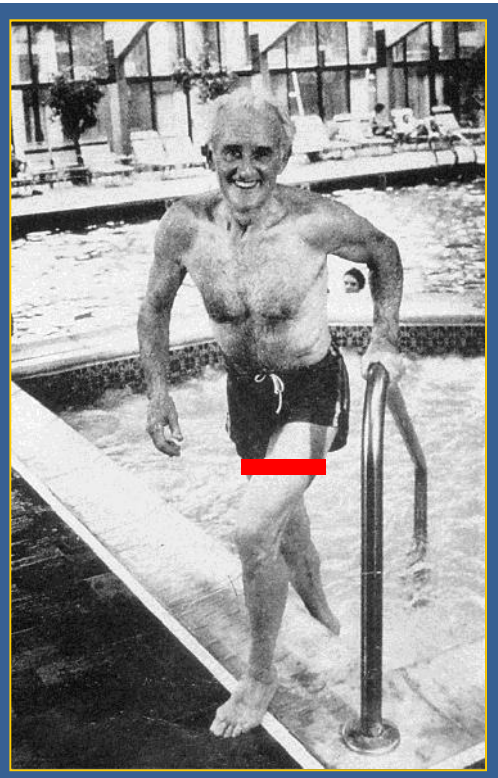
Dept. of Human Nutrition & Food Science, Texas W University, USA
ReGenera Research Group for Aging Intervention, Italy

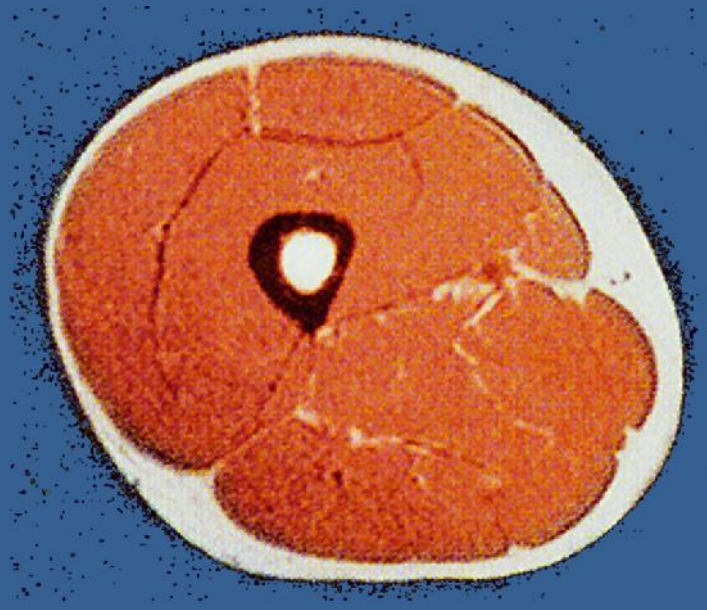
Body composition changes and aging

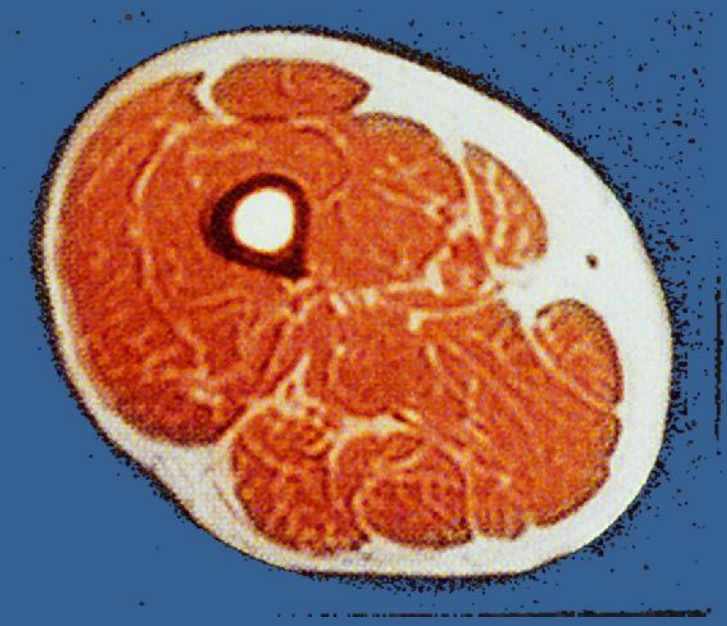


Short KR Curr Opin Clin Nutr Metab Care 2000;3:39-44


Age
Skeletal Muscle—Single Muscle Fiber
Endomysium
Striations
Sarcolemma
Sarcoplasm
Filaments
Nuclei
Myofibrils

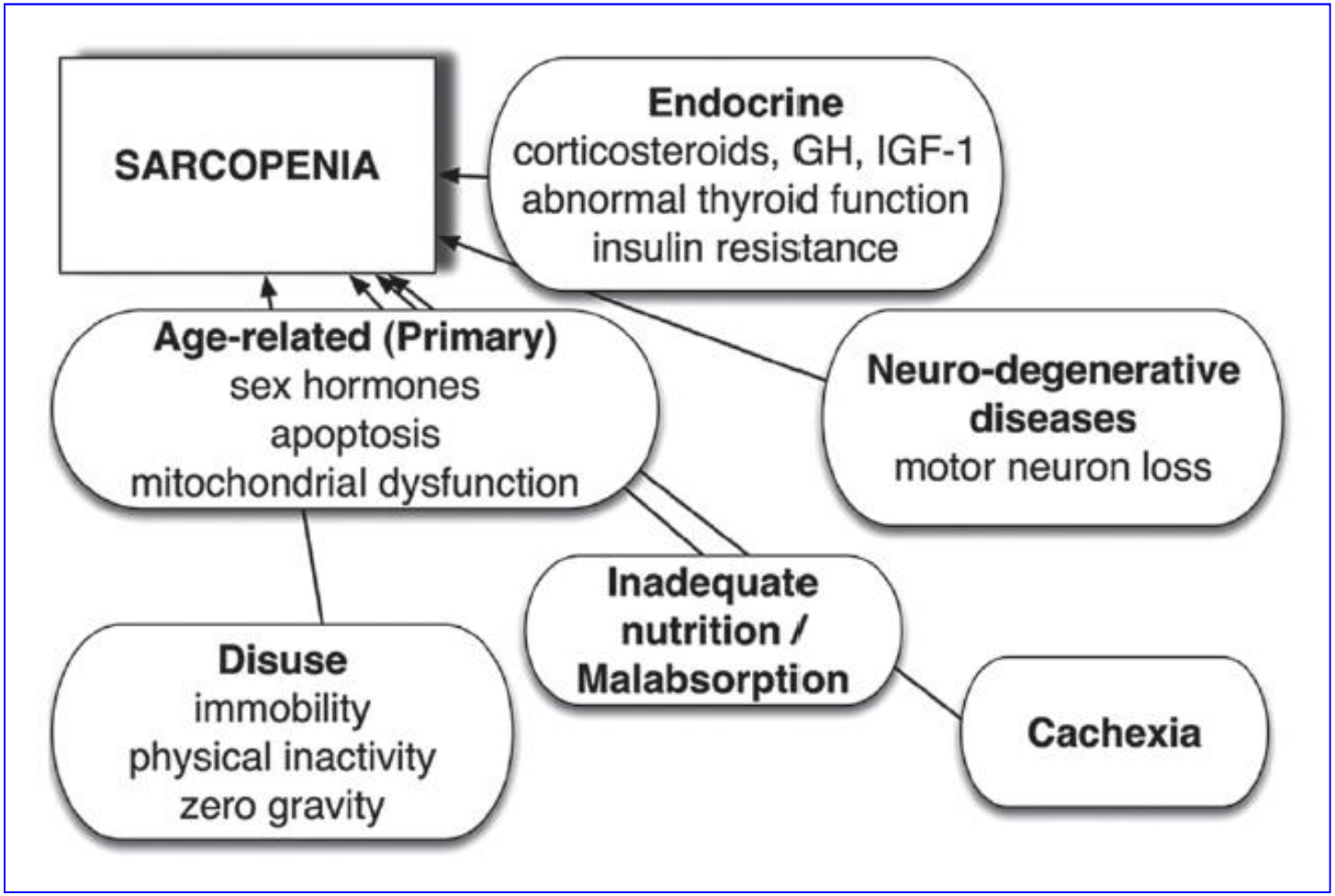






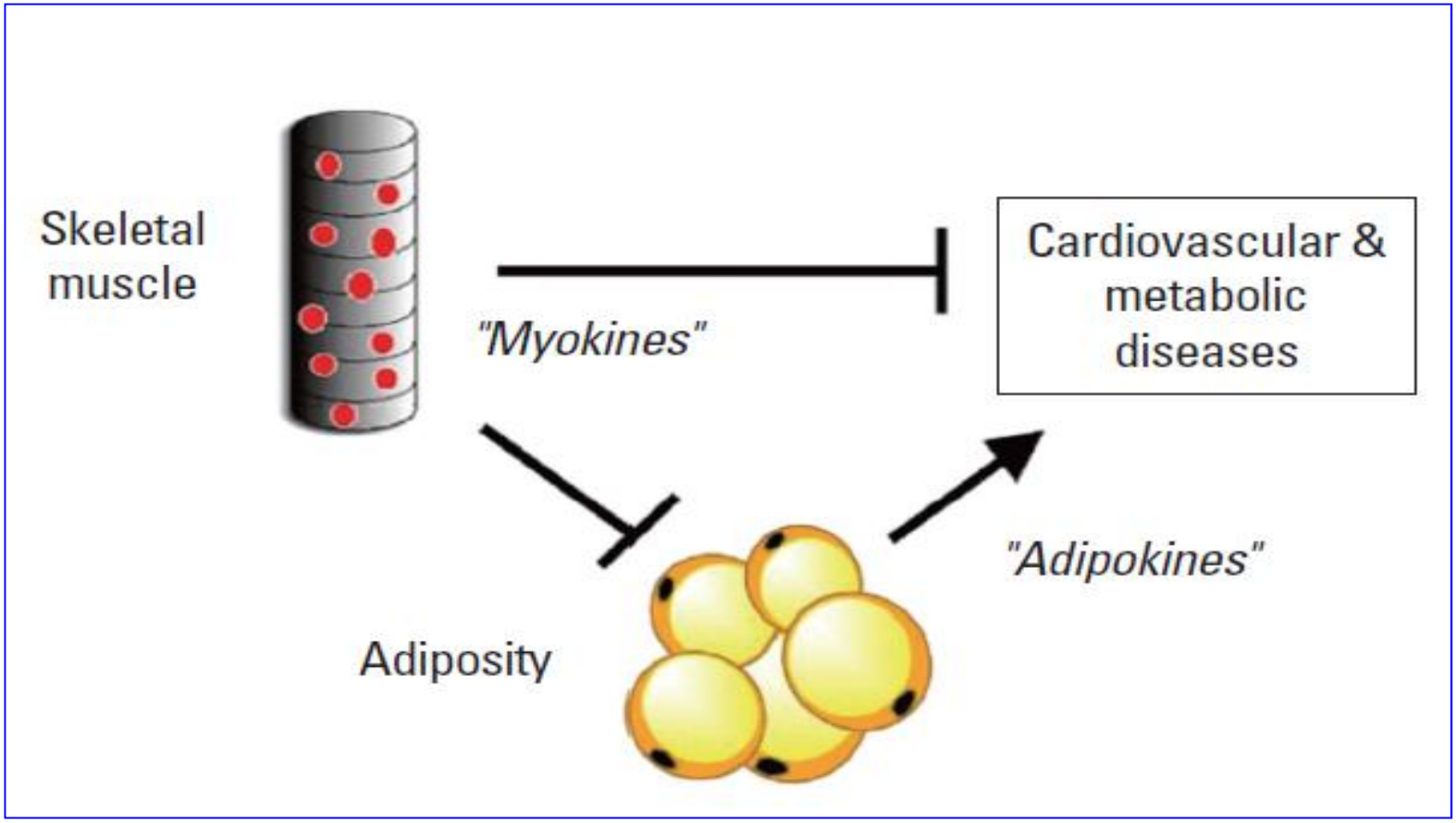
Sarcopenia: Definition, Epidemiology, and Pathophysiology

J Bone Metab 2013;20:1-10



Sarcopenia: Definition, Epidemiology, and Pathophysiology

J Bone Metab 2013;20:1-10



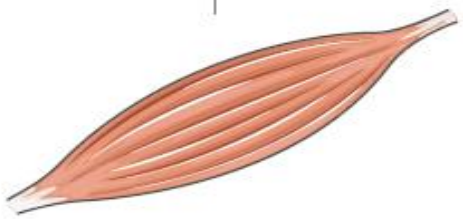
Adipo-Myokines: Two Sides of the Same Coin—Mediators of Inflammation and Mediators of Exercise

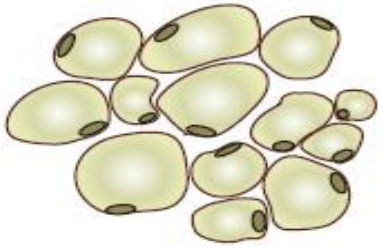
Mediators of Inflammation, 2013

Myokines	
BDNF	[135]
IL-7	[138, 139]
IL-15	[46, 138]
Irisin	
LIF	
Myonectin	[86]
Secretome studies	[25–29, 147, 148]

Adipo-myokines	
ANGPTL4	[133, 134]
FGF21	[137]
Fstl1	[111]
IL-6	[138]
IL-8	[140]
MCP-1	[12]
Myostatin	(Table 3)
PAI-1	[142]
PEDF	[141]
VEGF	(Table 3)

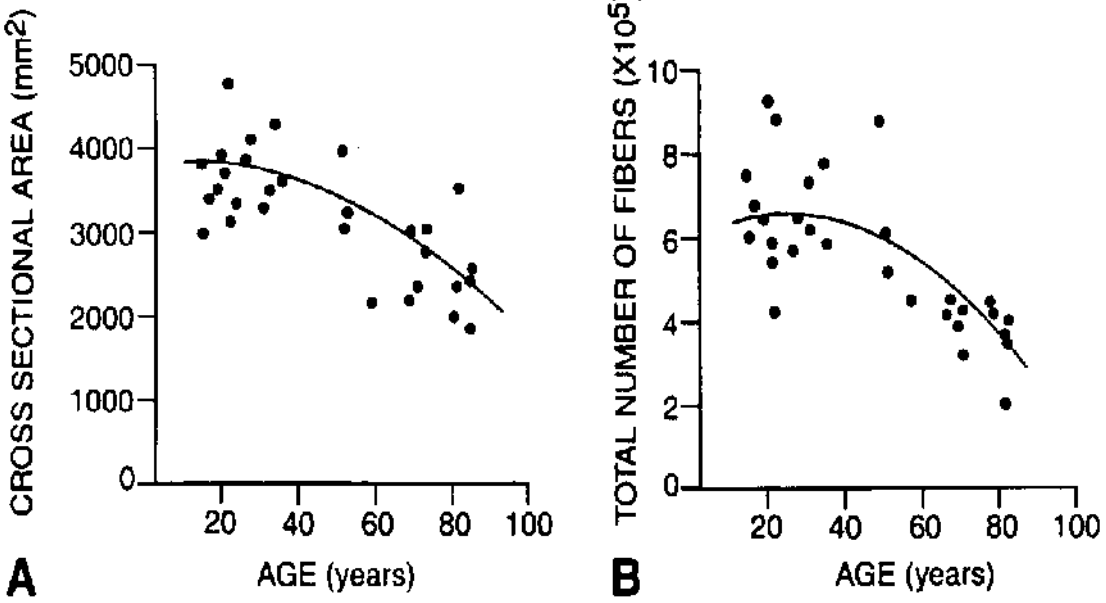
Adipokines	
Adiponec tin	[143, 144]
Leptin	[146]
Resistin	[145]
Secretome studies	[149–156]





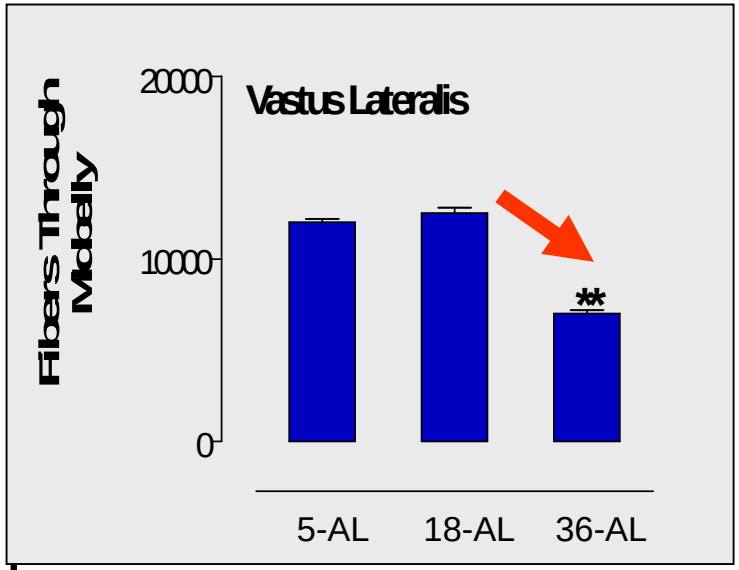
Is there skeletal muscle fiber loss with age in humans and animals?

Humans



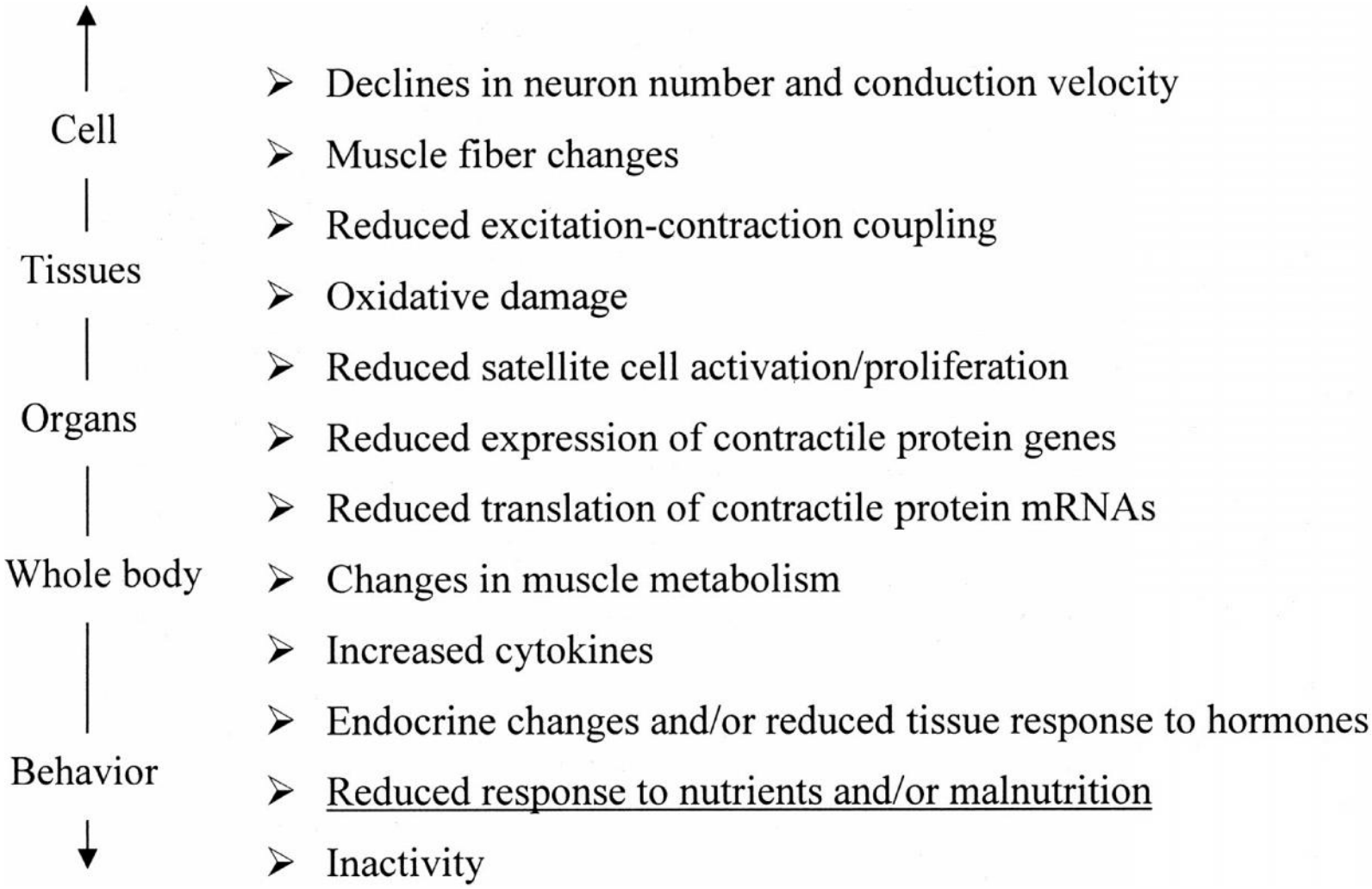
Lexell J, Taylor CC, Sjostrom M. What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. J Neurol Sci. 1988 Apr;84(2-3):275-94.

Animals



Bua EA, McKiernan SH, Wanagat J, McKenzie D, Aiken JM. Mitochondrial abnormalities are more frequent in muscles undergoing sarcopenia. J Appl Physiol. 2002 Jun;92(6):2617-24.

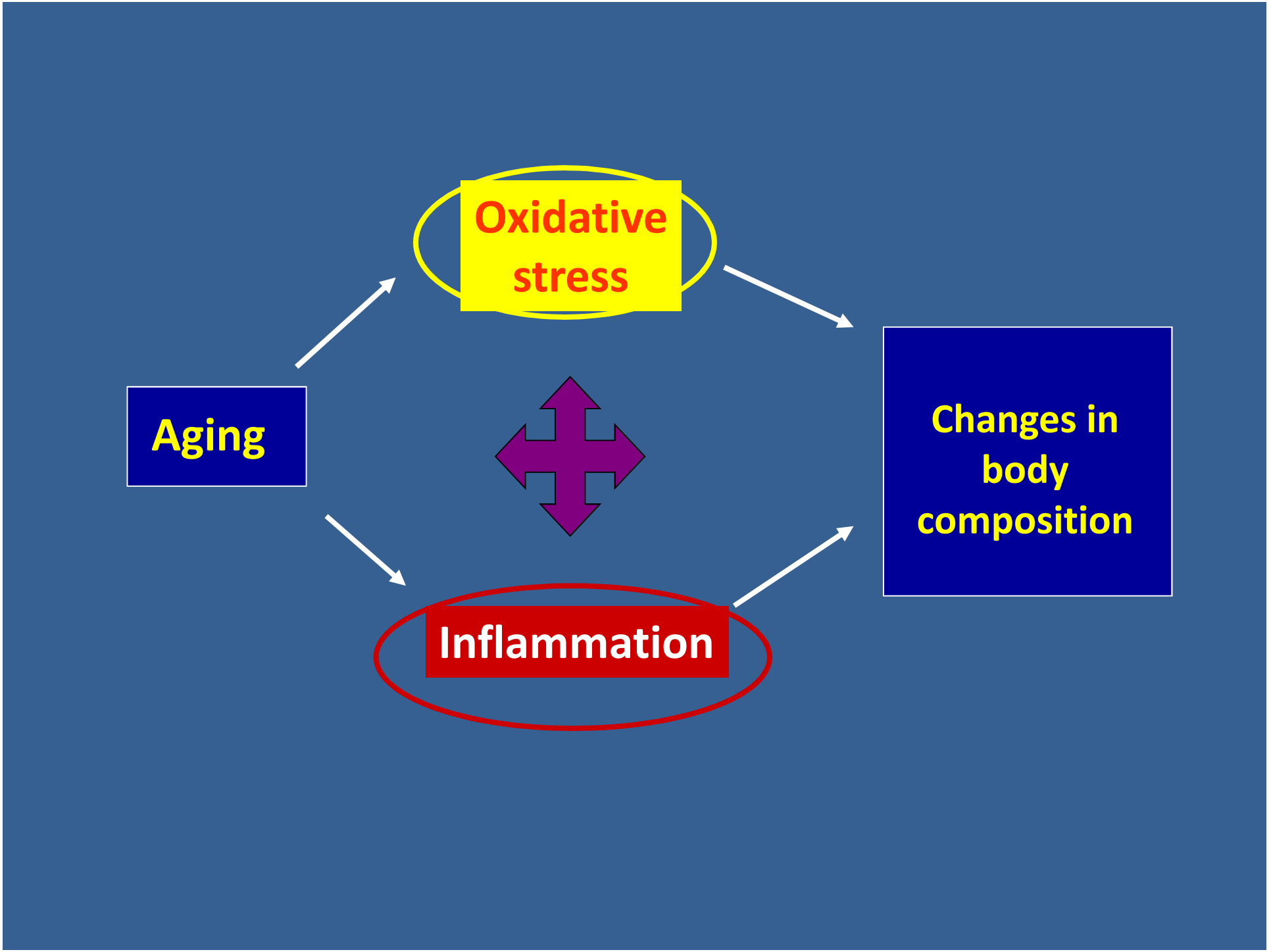
A partial list of mechanisms/consequences of sarcopenia.



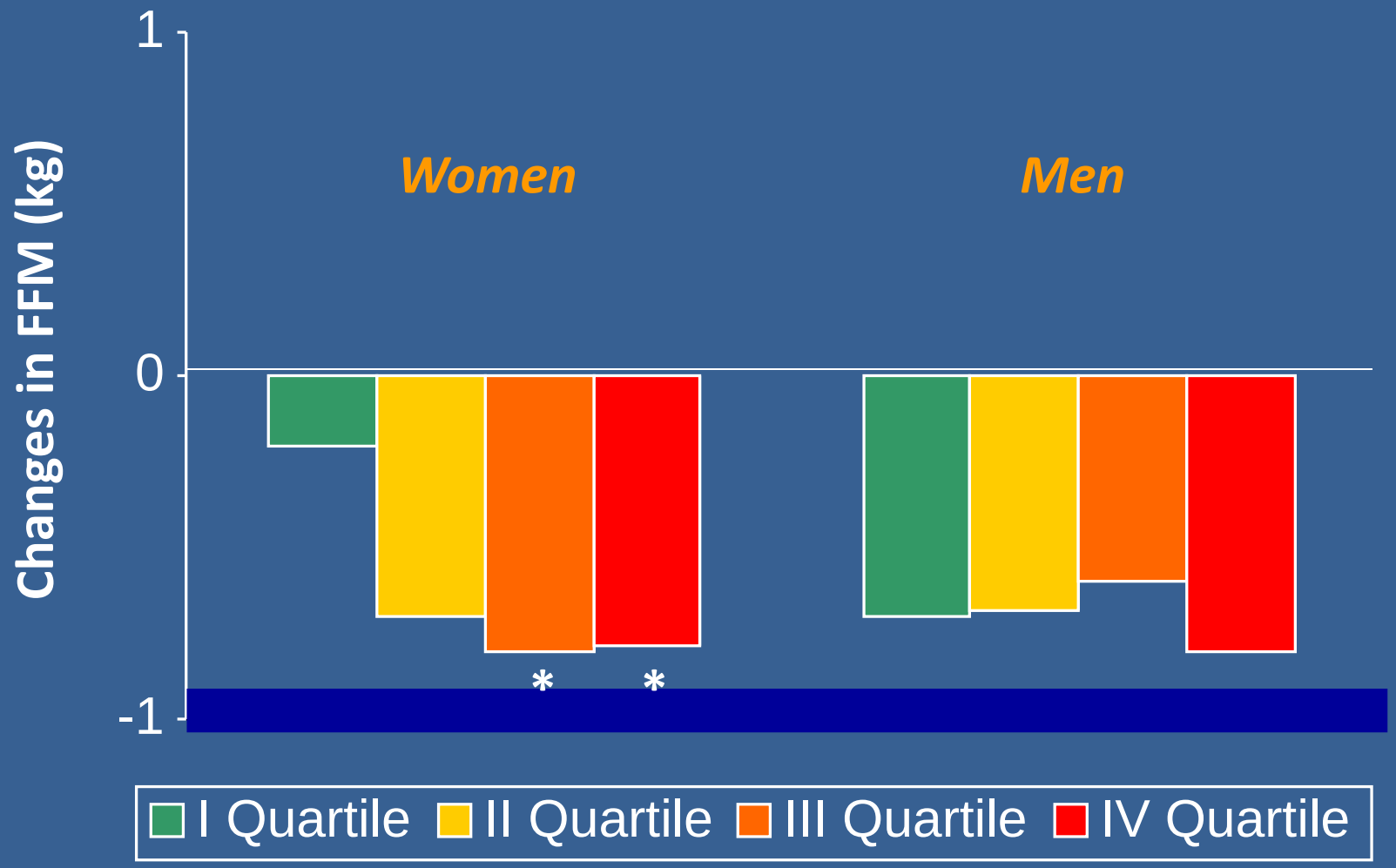
Paddon-Jones D et al. Am J Clin Nutr 2008;87:1562S-1566S

The American Journal of Clinical Nutrition

©2008 by American Society for Nutrition


Oxidative stress
Aging
Changes in body composition
Inflammation

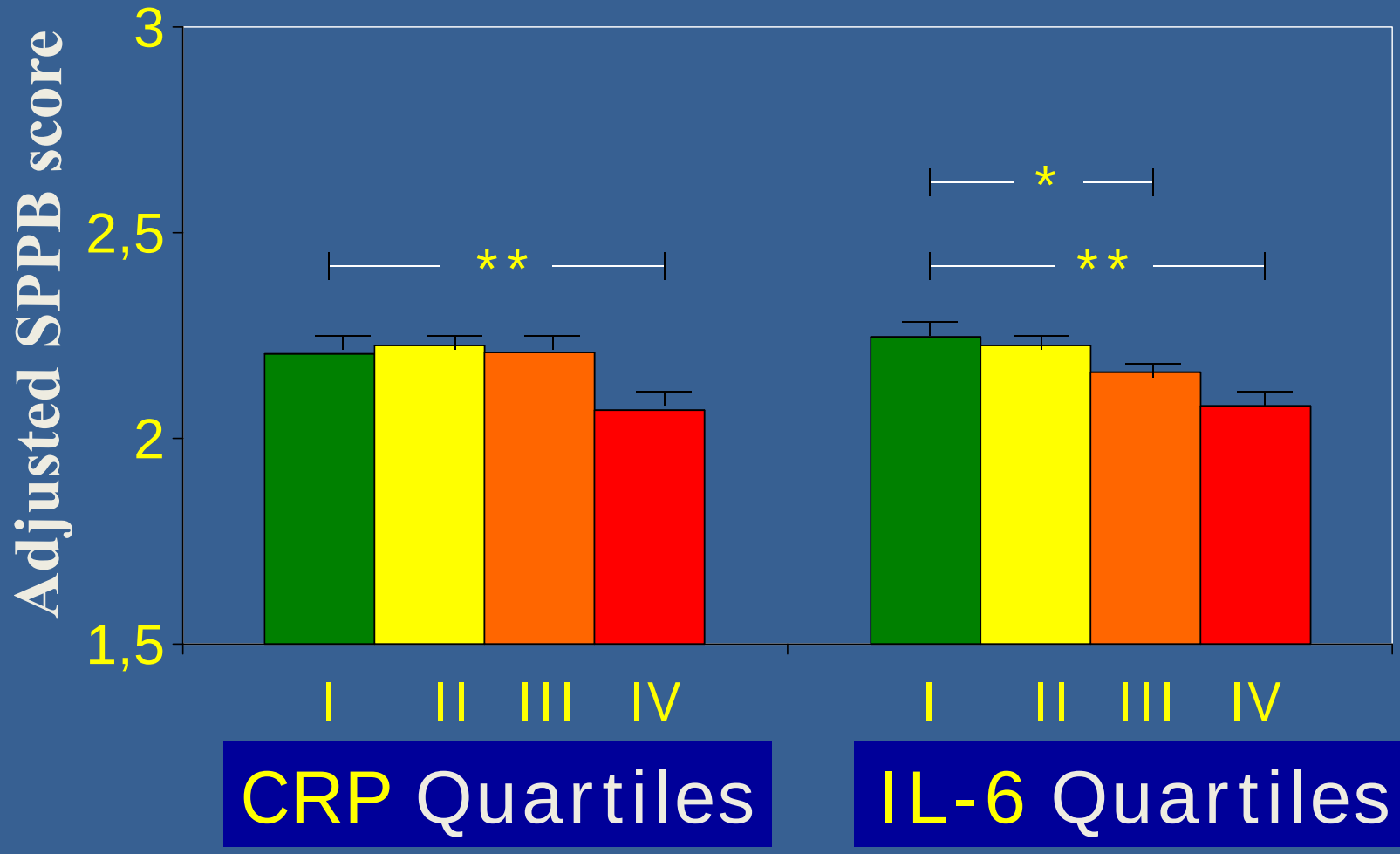
Two-year changes in fat-free mass (FFM) by IL-6 quartiles in the Framingham Heart Study



* p<0.05

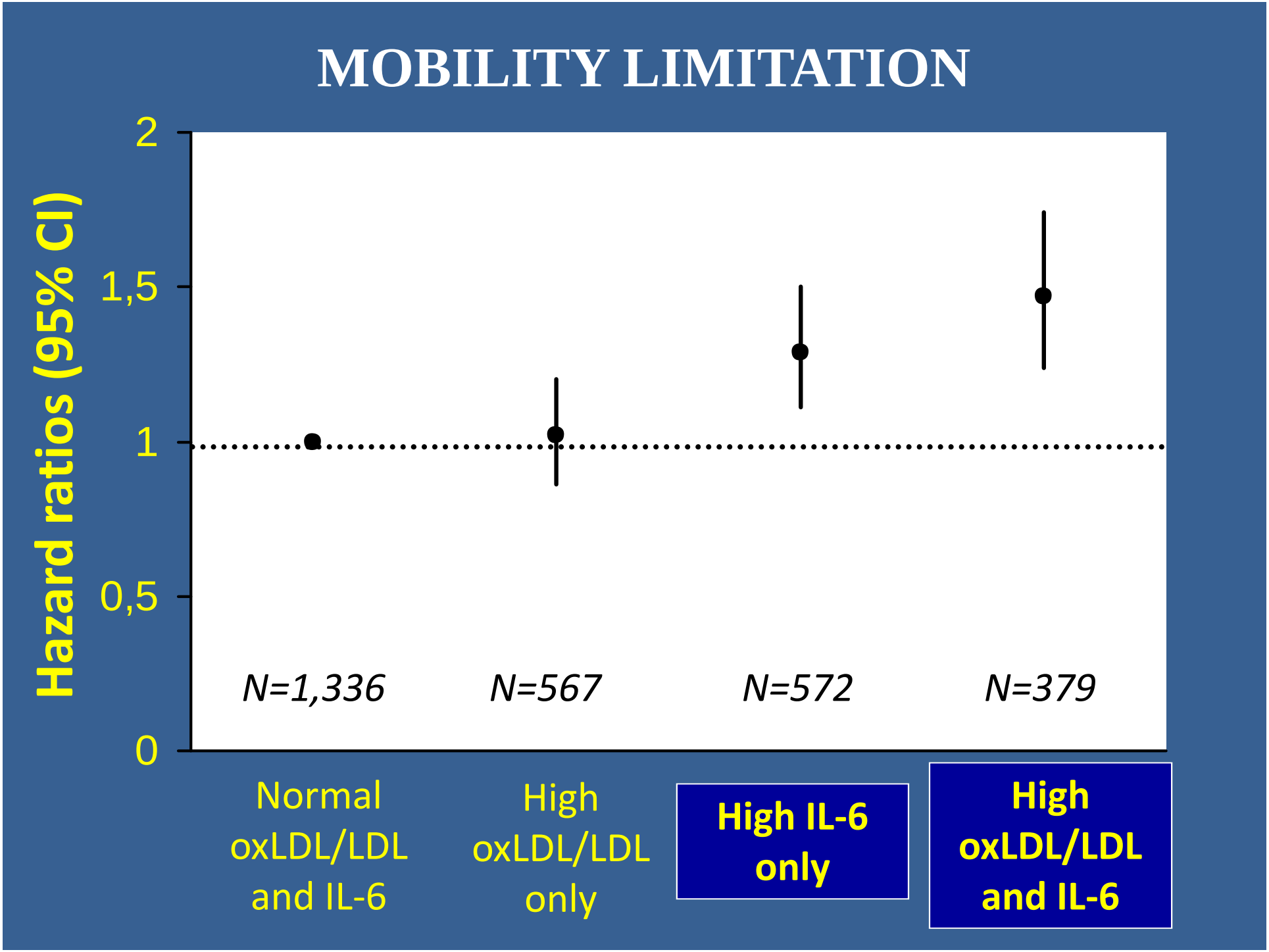
Payette H J Am Geriatr Soc 2003;51:1237-1243

Short Physical Performance Battery



Adjusted for sociodemographics, comorbidities, biological markers and medications

MOBILITY LIMITATION



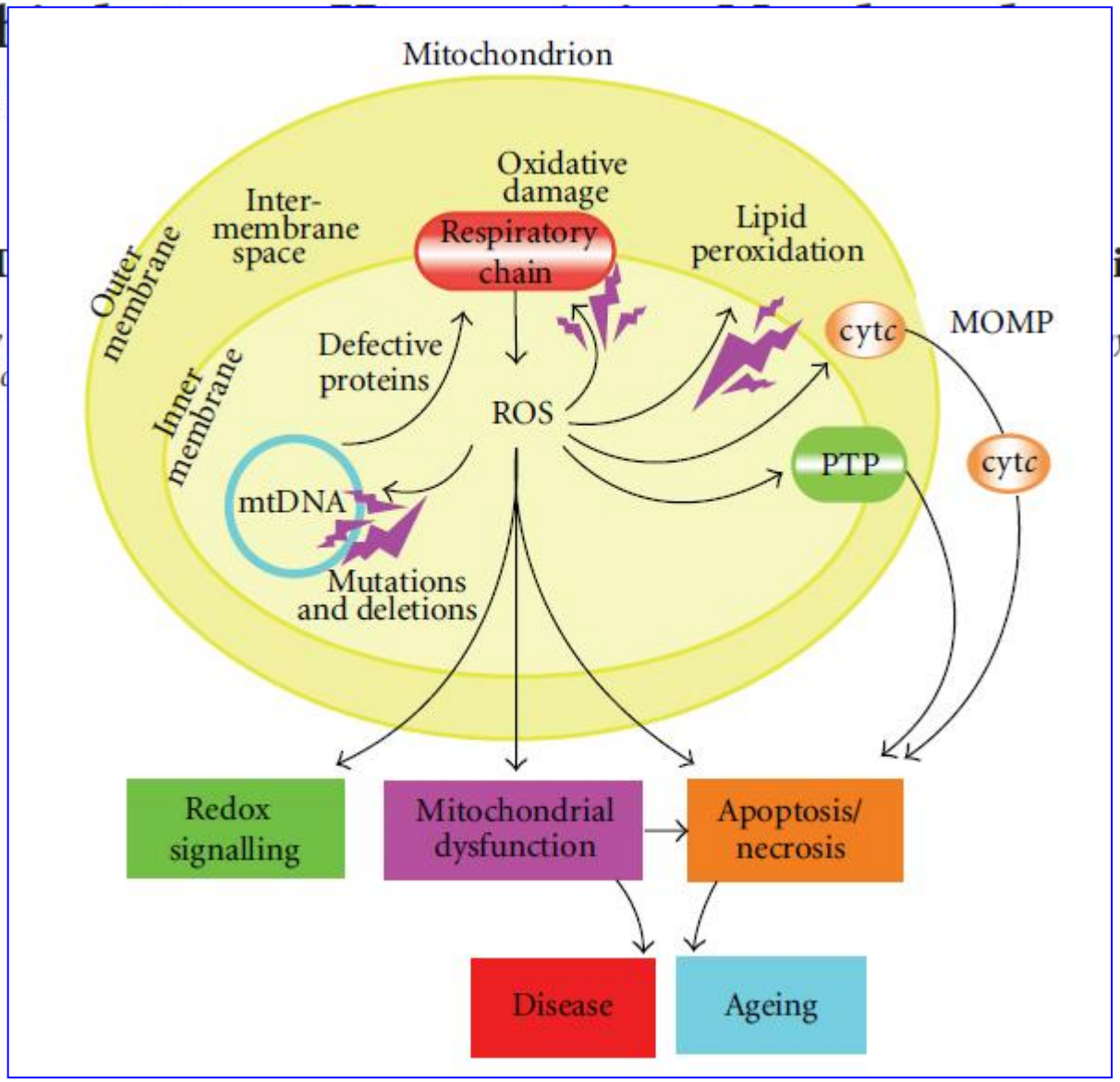
Hindawi Publishing Corporation
Oxidative Medicine and Cellular Longevity
Volume 2012, Article ID 830257, 13 pages
doi:10.1155/2012/830257

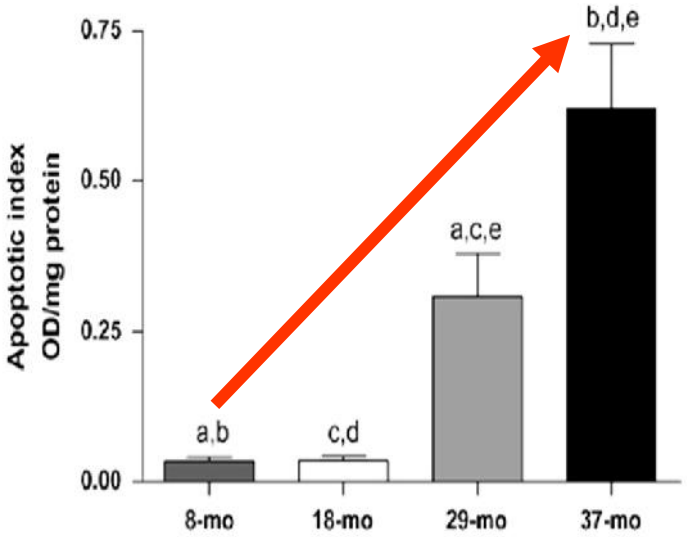
Review Article

Relationsh
Oxidative

Enrico I **ico**

Laboratory *y and Biotechnology,*
University





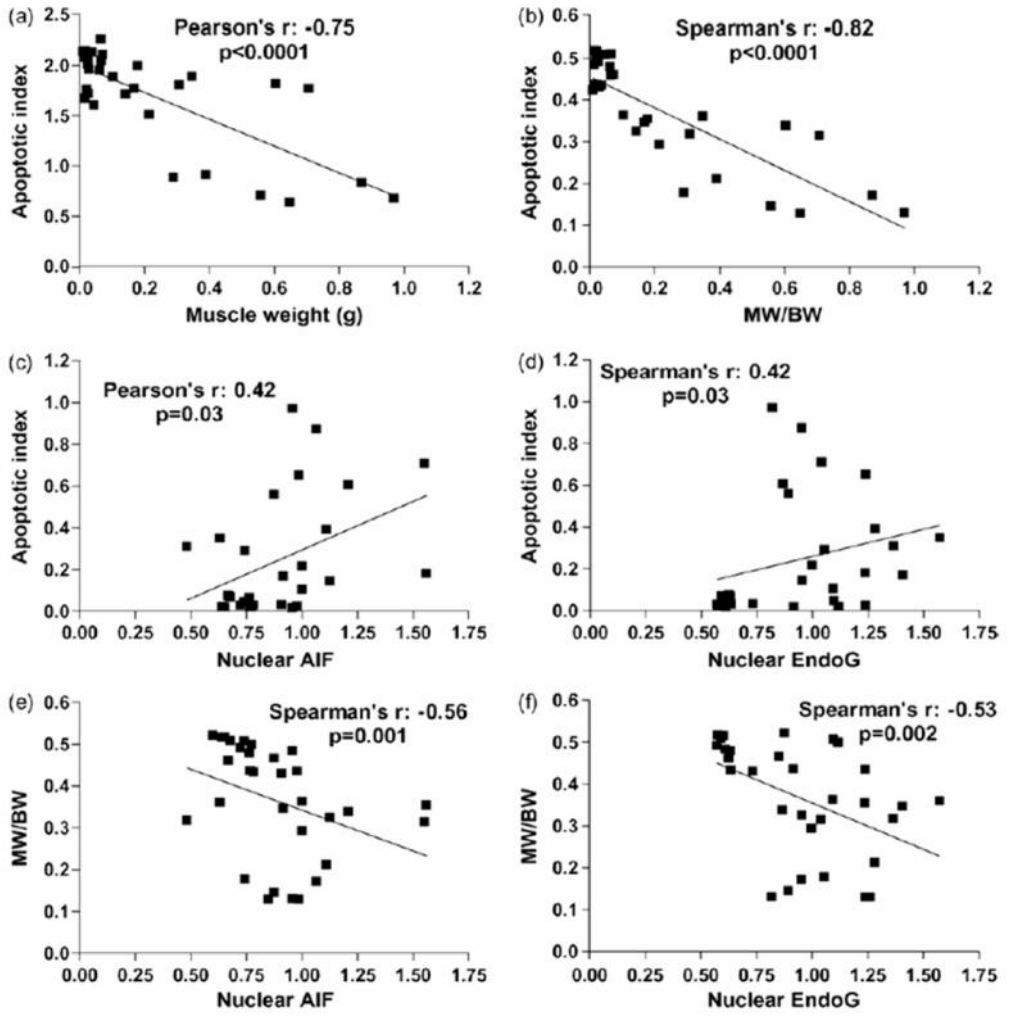
Mitochondrial apoptotic signaling is elevated in rat gastrocnemius muscle at **advanced age**, likely contributing to the age-related muscle loss. Activation of mitochondrial apoptotic signaling may be due to modification of the Bcl-2 proteins pattern of expression, possibly supported by enhanced levels of oxidative and nitrosative stress.

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

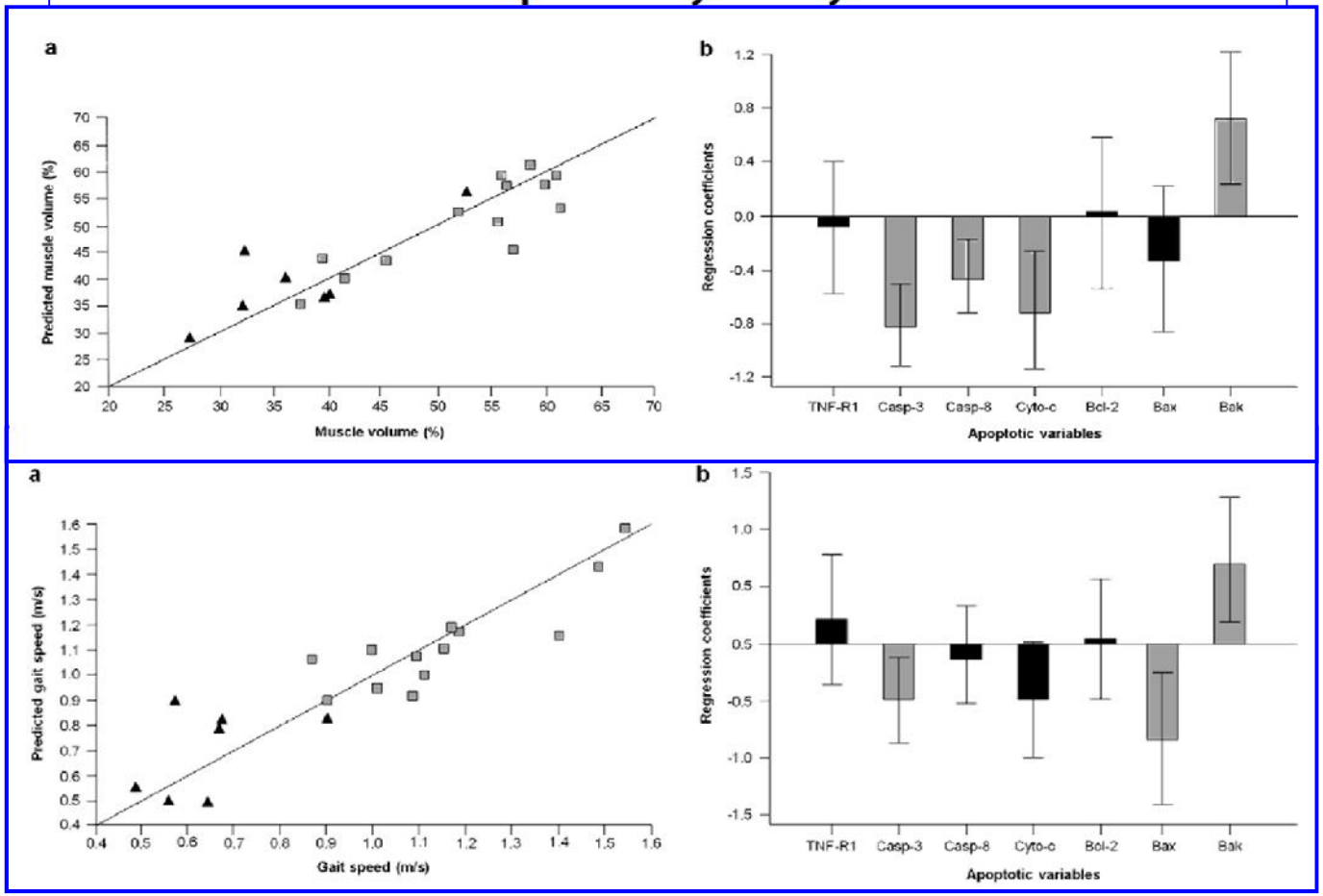
journal homepage: www.elsevier.com/locate/mechagedev

Age-related activation of mitochondrial caspase-independent apoptotic signaling in rat gastrocnemius muscle



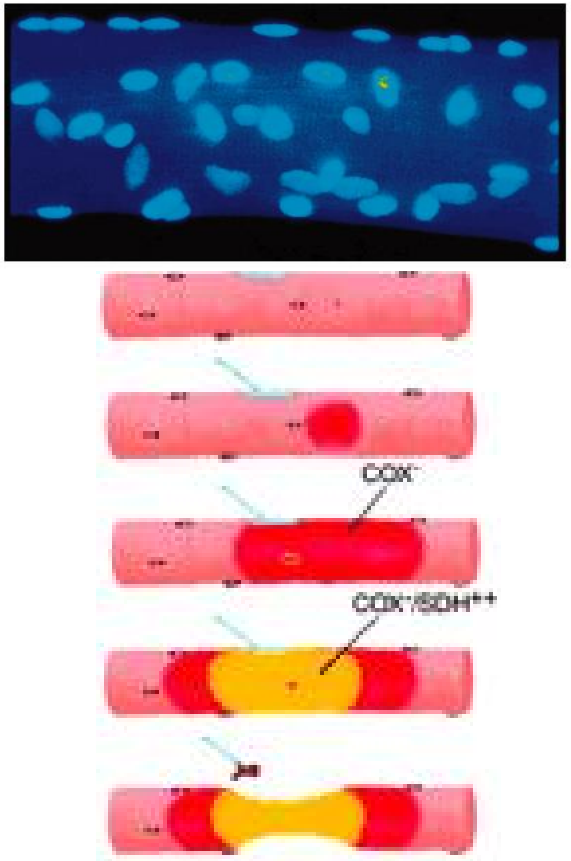
February 28, 2012 PLoS one

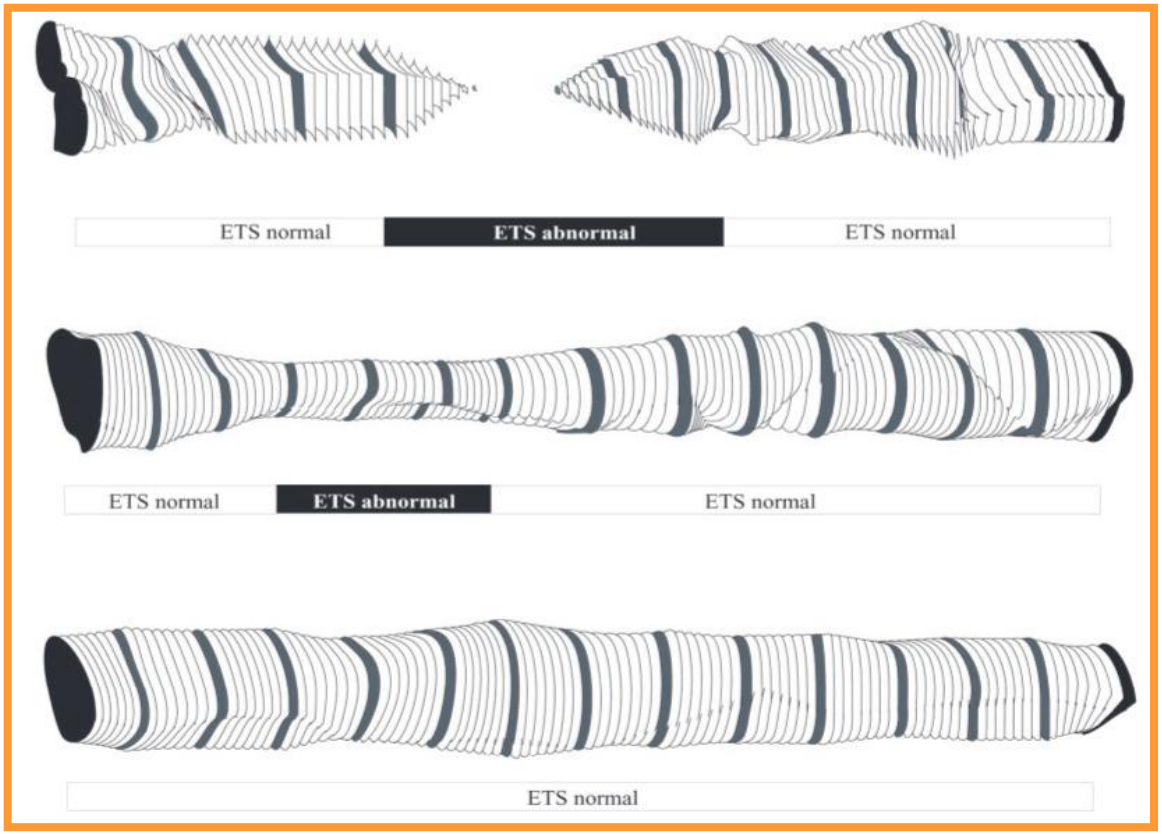
Skeletal Muscle Apoptotic Signaling Predicts Thigh Muscle Volume and Gait Speed in Community-Dwelling Older Persons: An Exploratory Study



This study shows for the first time that apoptotic signaling is correlated with indices of sarcopenia (i.e., decreased muscle mass and function) in a cohort of relatively healthy, community-dwelling older persons.

Oxidative damage, mtDNA deletions, and ETC abnormalities are co-localized along a single muscle fiber and exhibit atrophy





Wanagat et al. 2001. Mitochondrial DNA deletion mutations colocalize with segmental electron transport system abnormalities, muscle fiber atrophy, fiber splitting, and oxidative damage in sarcopenia. *Faseb J.* 15:322-32

Bua EA, McKiernan SH, Wanagat J, McKenzie D, Aiken JM. Mitochondrial abnormalities are more frequent in muscles undergoing sarcopenia. J Appl Physiol. 2002 Jun;92(6):2617-24.

The Journal of Nutrition, Health & Aging©
Volume 15, Number 8, 2011

JNHA: NUTRITION

NUTRITION IN THE AGE-RELATED DISABLEMENT PROCESS

M. INZITARI[1,2], E. DOETS[3], B. BARTALI[4], V. BENETOU[5], M. DI BARI[6], M. VISSER[7], S. VOLPATO[8], G. GAMBASSI[9], E. TOPINKOVA[10], L. DE GROOT[3], A. SALVA[1] FOR THE INTERNATIONAL ASSOCIATION OF GERONTOLOGY AND GERIATRICS (IAGG) TASK FORCE FOR NUTRITION IN THE ELDERLY[11]

Associations of specific dietary factors with muscle mass and function

Dietary factor	Evidence	Some open questions
Proteins	• Inadequate intake may accelerate the loss of lean mass (43) • Protein anabolism can be stimulated by increased essential amino acid availability (44)	• Potential attenuation of the loss of lean mass with higher protein intakes? • Optimal level and type of proteins?
Vitamin D	• Low serum vitamin D has been associated with poor and decreasing muscle strength (45) • Vitamin D supplementation trial showed a substantial increase in quadriceps strength and functional performance in older persons (46)	• Observational studies are inconsistent (47)
Magnesium	• Low serum magnesium has been associated with reduced muscle strength (48)	
Carotenoids	• Low serum carotenoids have been associated with poorer muscle strength in older adults (49)	
Selenium	• Low plasma selenium has been associated with poorer muscle strength in older adults (50)	

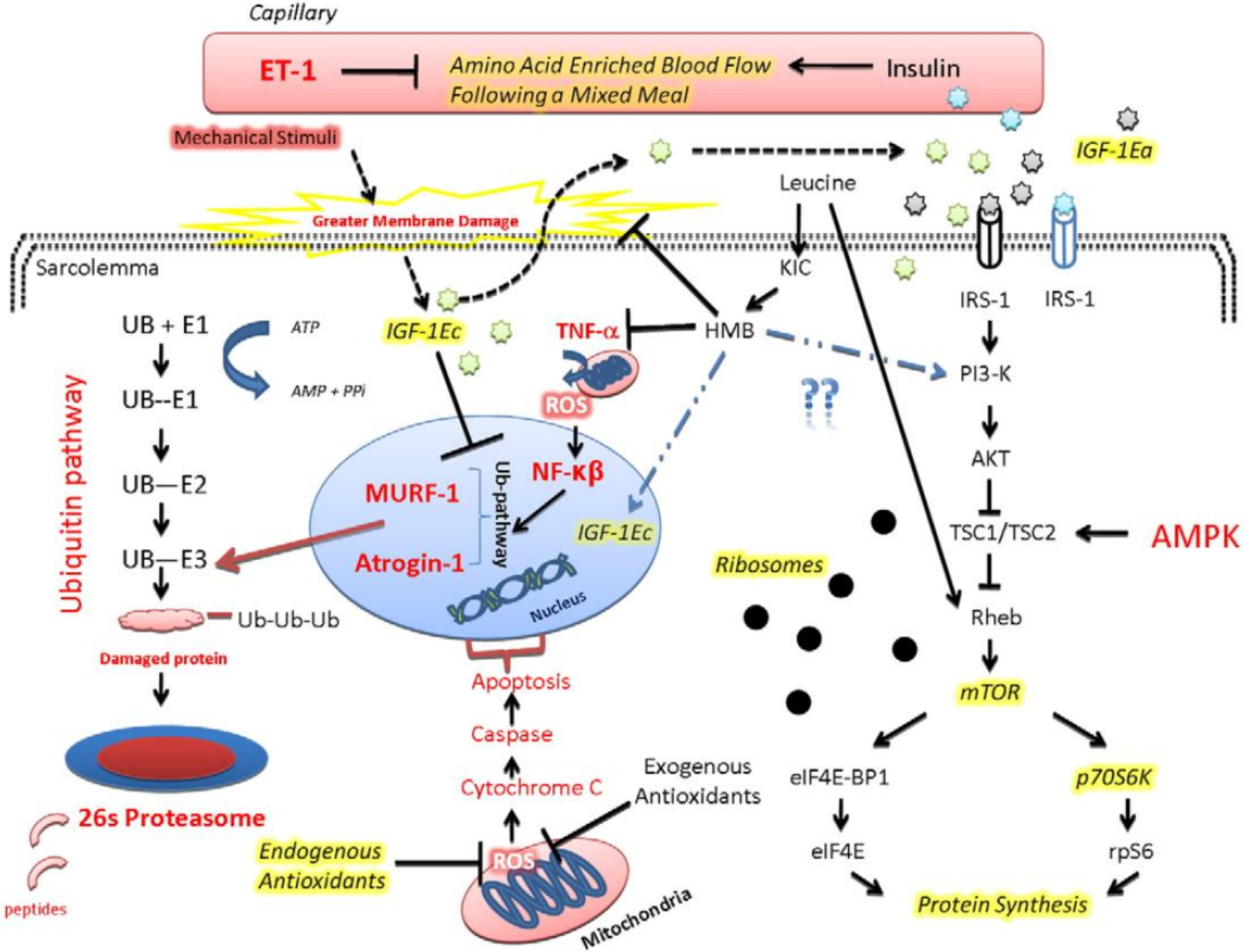
Available online at www.sciencedirect.com
ScienceDirect
Journal of Nutritional Biochemistry 21 (2010) 1 – 13
Journal of Nutritional Biochemistry

REVIEWS: CURRENT TOPICS

Dietary implications on mechanisms of sarcopenia: roles of protein, amino acids and antioxidants

Jeong-Su Kim*, Jacob M. Wilson, Sang-Rok Lee

Department of Nutrition, Food and Exercise Sciences, College of Human Sciences, The Florida State University, Tallahassee, FL 32306-1493, USA


Capillary
ET-1
Amino Acid Enriched Blood Flow Following a Mixed Meal
Insulin
Mechanical Stimuli
Greater Membrane Damage
IGF-1Ea
Leucine
Sarcolemma
KIC
IRS-1
IRS-1
UB + E1
ATP
AMP + PPi
IGF-1Ec
TNF-α
HMB
ROS
??
PI3-K
AKT
Ubiquitin pathway
UB--E1
UB—E2
UB—E3
MURF-1
Ub-pathway
NF-κβ
IGF-1Ec
Atrogin-1
Nucleus
TSC1/TSC2
AMPK
Ribosomes
Ub-Ub-Ub
Damaged protein
Rheb
Apoptosis
mTOR
Caspase
Exogenous Antioxidants
eIF4E-BP1
p70S6K
Cytochrome C
26s Proteasome
Endogenous Antioxidants
ROS
eIF4E
rpS6
peptides
Mitochondria
Protein Synthesis

Journal of Aging Research
Home | Editorial Board | Author Guidelines | Aims and Scope | Submit a Manuscript

Hindawi Publishing Corporation
Journal of Aging Research
Volume 2012, Article ID 316943, 8 pages
doi:10.1155/2012/316943

Review Article

Rationale for Antioxidant Supplementation in Sarcopenia

Francesco Cerullo,[1] Giovanni Gambassi,[1] and Matteo Cesari[2]

The Journal of Nutrition
Nutrient Physiology, Metabolism, and Nutrient-Nutrient Interactions

Antioxidant Supplementation Restores Defective Leucine Stimulation of Protein Synthesis in Skeletal Muscle from Old Rats[1,2]

Barbara Marzani,[3] Michèle Balage,[3]* Annie Vénien,[4] Thierry Astruc,[4] Isabelle Papet,[3] Dominique Dardevet,[3] and Laurent Mosoni[3]

[3]INRA, Centre de Clermont-Ferrand–Theix, UMR 1019, Unité Nutrition Humaine, Saint Genès Champanelle, F-63122 and Univ Clermont 1, UFR Médecine, UMR 1019, Unité Nutrition Humaine, Clermont-Ferrand, F-63001 France and [4]INRA, UR370 QuaPA, F-63122 Saint-Genès Champanelle, France

Aging is characterized by a progressive loss of muscle mass that could be partly explained by a defect in the anabolic effect of food intake. We previously reported that this defect resulted from a decrease in the protein synthesis response to leucine in muscles from old rats. Because aging is associated with changes in oxidative status, we hypothesized that reactive oxygen species–induced oxidative damage may be involved in the impairment of the anabolic effect of leucine with age. The present study assessed the effect of antioxidant supplementation on leucine-regulated protein metabolism in muscles from adult and old rats. Four groups of 8- and 20-mo-old male rats were supplemented or not for 7 wk with an antioxidant mixture containing rutin, vitamin E, vitamin A, zinc, and selenium. At the end of supplementation, muscle protein metabolism was examined in vitro using epitrochlearis muscles incubated with increasing leucine concentrations. In old rats, the ability of leucine to stimulate muscle protein synthesis was significantly decreased compared with adults. This defect was reversed when old rats were supplemented with antioxidants. It was not related to increased oxidative damage to 70-kDa ribosomal protein S6 kinase that is involved in amino acid signaling. These effects could be mediated through a reduction in the inflammatory state, which decreased with antioxidant supplementation. Antioxidant supplementation could benefit muscle protein metabolism during aging, but further studies are needed to determine the mechanism involved and to establish if it could be a useful nutritional tool to slow down sarcopenia with longer supplementation. J. Nutr. 138: 2205–2211, 2008.

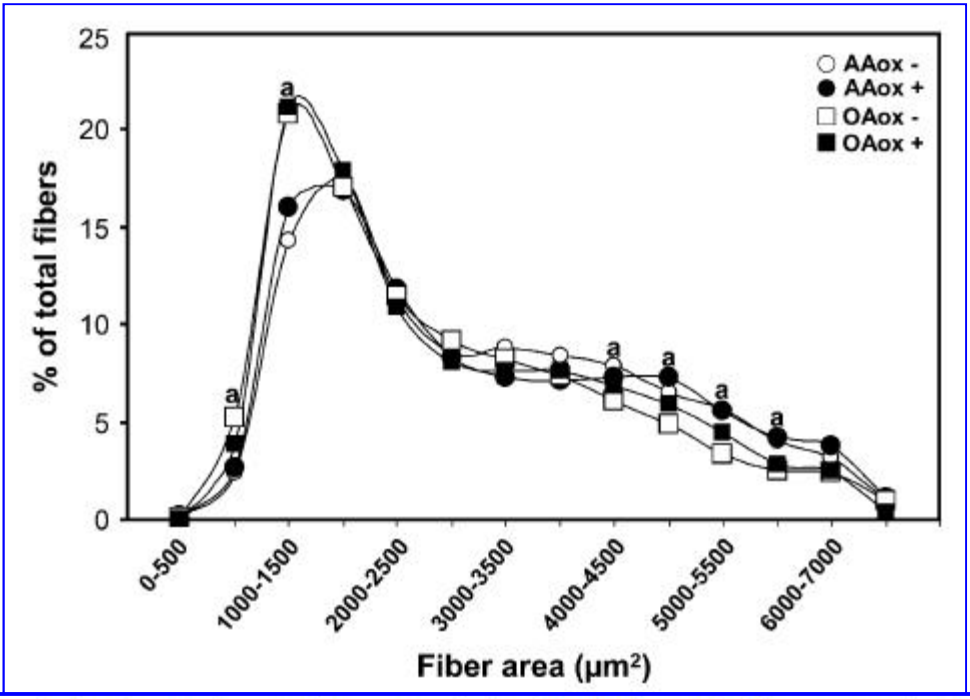


TABLE 2 Body, skeletal muscle, and organ weights in adult and old rats supplemented (Aox+) or not (Aox−) with antioxidants[1]

	Adult		Old		
	Aox−	Aox+	Aox−	Aox+	2-Way ANOVA[2]
Body weight, *g*	692 ± 11	704 ± 12	675 ± 24	681 ± 23	
Gastrocnemius, *g*	5.96 ± 0.15	6.11 ± 0.16	4.95 ± 0.08	5.20 ± 0.11	A
Tibialis anterior, *g*	1.98 ± 0.05	2.04 ± 0.06	1.72 ± 0.06	1.81 ± 0.05	A
EDL, *mg*	510 ± 14	508 ± 12	439 ± 11	458 ± 10	A
Soleus, *mg*	415 ± 11	433 ± 13	360 ± 15	371 ± 18	A
Heart, *g*	1.69 ± 0.02	1.60 ± 0.03	1.78 ± 0.09	1.59 ± 0.07	D
Liver, *g*	16.9 ± 0.5	16.9 ± 0.4	16.0 ± 0.8	16.1 ± 0.6	
Spleen, *g*	1.18 ± 0.05	1.10 ± 0.03	1.59 ± 0.08	1.42 ± 0.05	A, D
Kidneys, *g*	3.42 ± 0.10	3.17 ± 0.07	4.94 ± 0.70	4.05 ± 0.39	A

[1] Values are means ± SEM, $n = 10–12$.
[2] A: Significant effect of age, $P < 0.005$; D: significant effect of diet, $P < 0.05$.

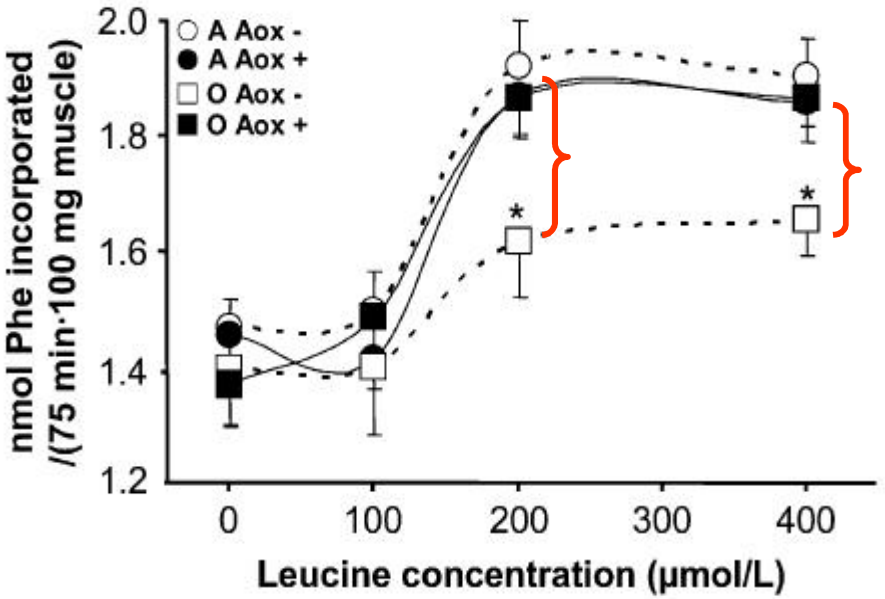


FIGURE 2 Dose-response curves for leucine stimulated muscle protein synthesis in adult (A) and old (O) rats supplemented (Aox+) or not (Aox−) with antioxidants for 7 wk. Rate of protein synthesis was measured as in vitro incorporation of ^{14}C phenylalanine into epitrochlearis muscles in the presence of increasing leucine concentrations.

Oxidation state of S6K. The carbonyl content, a marker of oxidative damages, detected by DNPH associated to S6K (expressed as a ratio to total S6K) was similar in adult and old rats and did not change by Aox supplementation (data not shown).

Free Radic Biol Med. 2005 August 15; 39(4): 549–557. doi:10.1016/j.freeradbiomed.2005.04.008.

Effect of antioxidant-enriched diets on glutathione redox status in tissue homogenates and mitochondria of the senescence-accelerated mouse

The main purpose of this study was to investigate whether consumption of diets enriched in antioxidants attenuates the level of oxidative stress in the senescence-accelerated mouse (SAM). In separate and independent studies, two different dietary mixtures, one enriched with vitamin E, vitamin C, L-carnitine, and lipoic acid (Diet I) and another diet including vitamins E and C and 13 additional ingredients containing micronutrients with bioflavonoids, polyphenols, and carotenoids (Diet II), were fed for 8 and 10 months, respectively. The amounts of glutathione (GSH) and glutathione disulfides (GSSG) and GSH:GSSG ratios were determined in plasma, tissue homogenates, and mitochondria isolated from five different tissues of SAM (P8) mice. Both diets had a reductive effect in plasma; however Diet I had relatively little effect on the glutathione redox status in tissue homogenates or mitochondria. Remarkably, Diet II caused a large increase in the amount of glutathione and a marked reductive shift in glutathione redox state in mitochondria. Overall, the effects of Diet II were tissue and gender specific. Results indicated that the glutathione redox state in mitochondria and tissues can be altered by supplemental intake of a relatively complex mixture of dietary antioxidants that contains substances known to induce phase 2 enzymes, glutathione, and antioxidant defenses. Whether corresponding attenuations occur in age-associated deleterious changes in physiological functions or life span remains unknown.

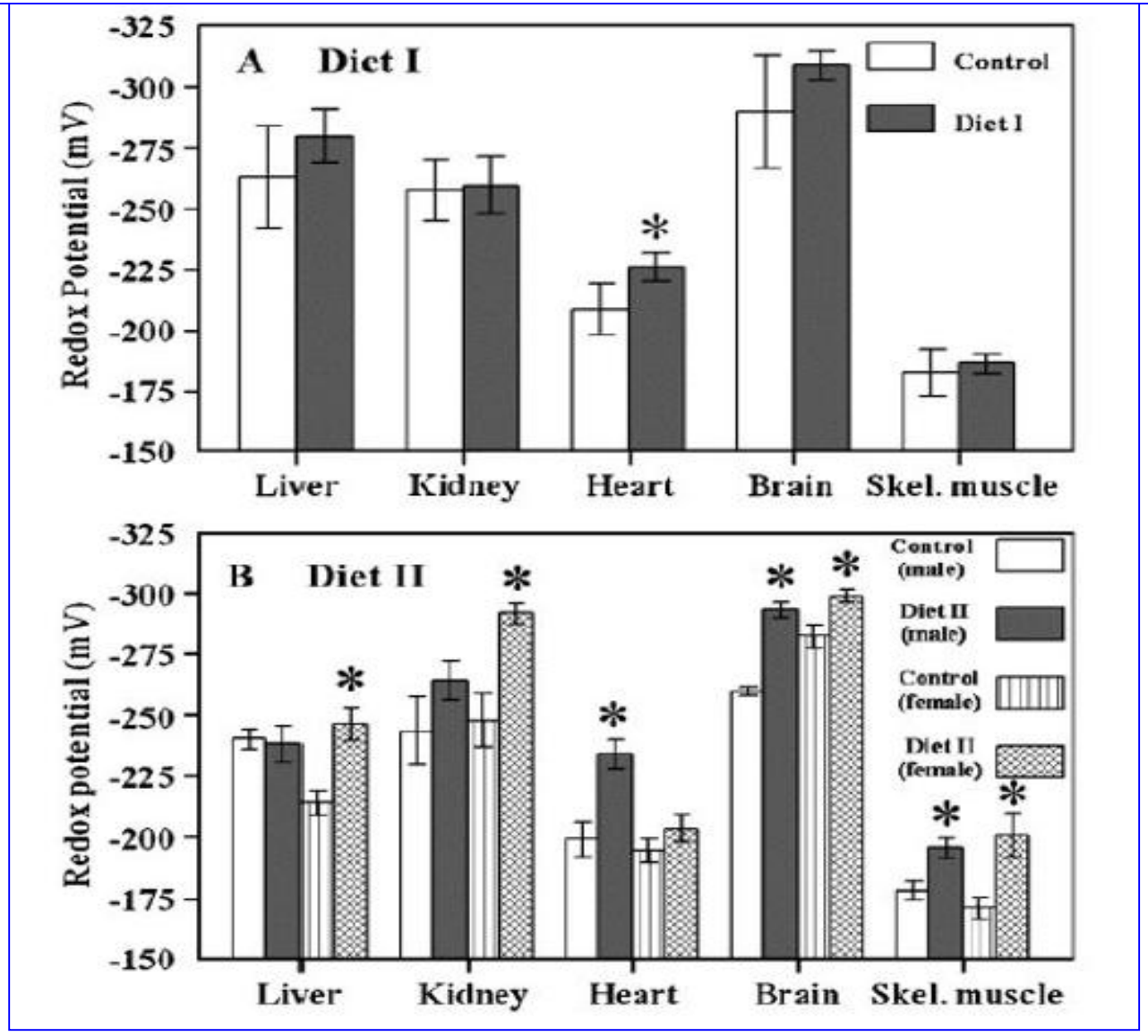
Free Radic Biol Med. 2005 August 15; 39(4): 549–557. doi:10.1016/j.freeradbiomed.2005.04.008.

Effect of antioxidant-enriched diets on glutathione redox status in tissue homogenates and mitochondria of the senescence-accelerated mouse

Component	Control	Diet I	Diet II
Protein	170	170	190
Fat	100	100	100
Vitamin E	200 ppm[b]	500 ppm[b]	500 ppm[b]
Vitamin C	<32 ppm	80 ppm[b]	80 ppm[b]
L-Carnitine	10 ppm[b]	300 ppm[b]	–
Lipoic acid	_[e]	125 ppm	–
±Broccoli[c]	–	–	15
±Rice bran[c]	–	–	10
Marine oil	–	–	8.8
Glutamine dipeptide[d]	–	–	5
Methionine[d]	–	–	1.7
±Selenium-yeast[a]	–	–	0.3
±Algae[a]	–	–	0.25
L-Threonine[d]	–	–	0.25
Lutein (5%)	–	–	0.15
Lycopene (5%)	–	–	0.15
Astaxanthin (8%)	–	–	0.094
β-Carotene (10%)	–	–	0.075
Curcumin	–	–	0.05

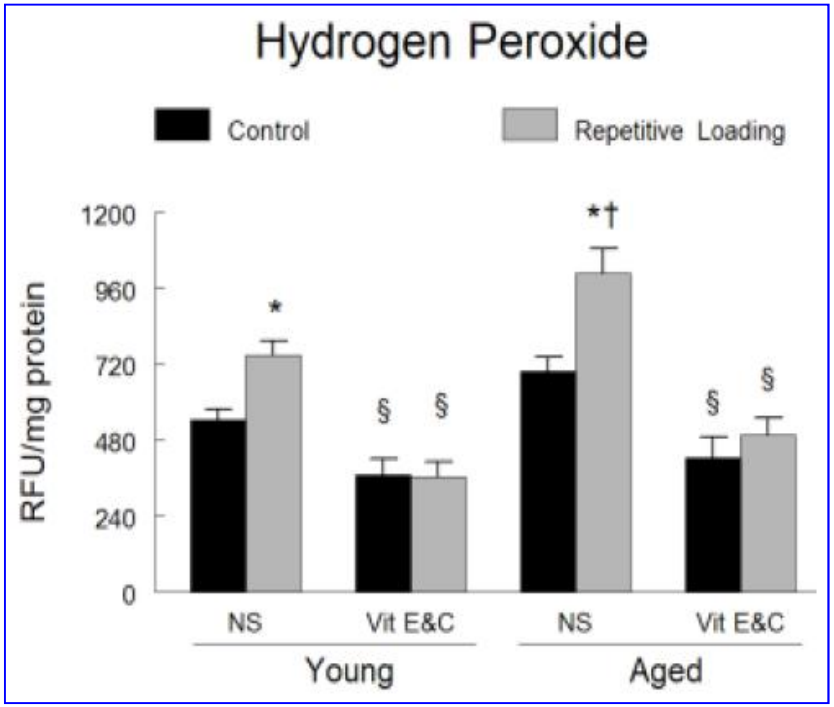
Free Radic Biol Med. 2005 August 15; 39(4): 549–557. doi:10.1016/j.freeradbiomed.2005.04.008.

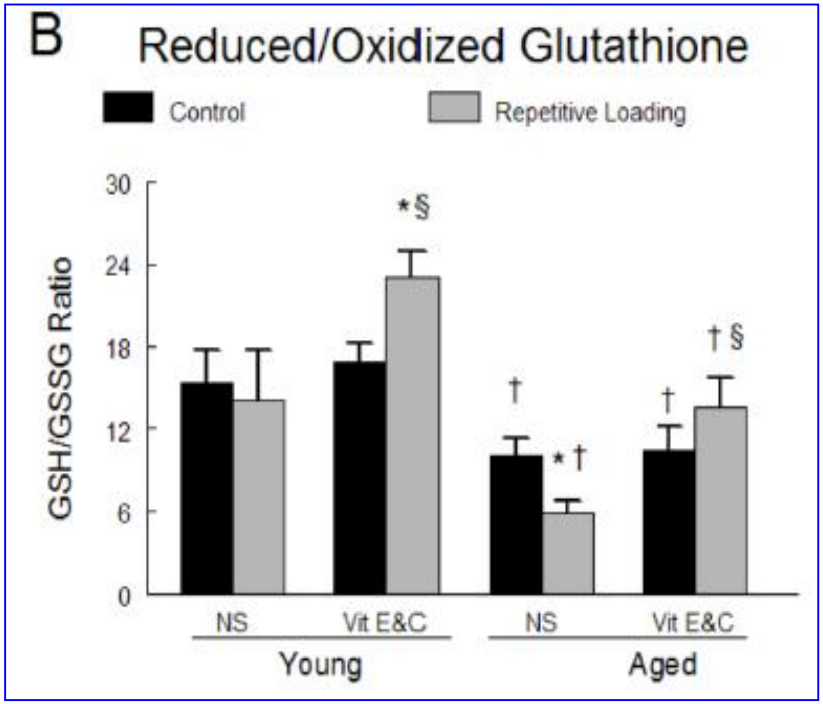
Effect of antioxidant-enriched diets on glutathione redox status in tissue homogenates and mitochondria of the senescence-accelerated mouse



Exp Gerontol. 2010 November ; 45(11): 882–895. doi:10.1016/j.exger.2010.08.002.

Vitamin E and C supplementation reduces oxidative stress, improves antioxidant enzymes and positive muscle work in chronically loaded muscles of aged rats



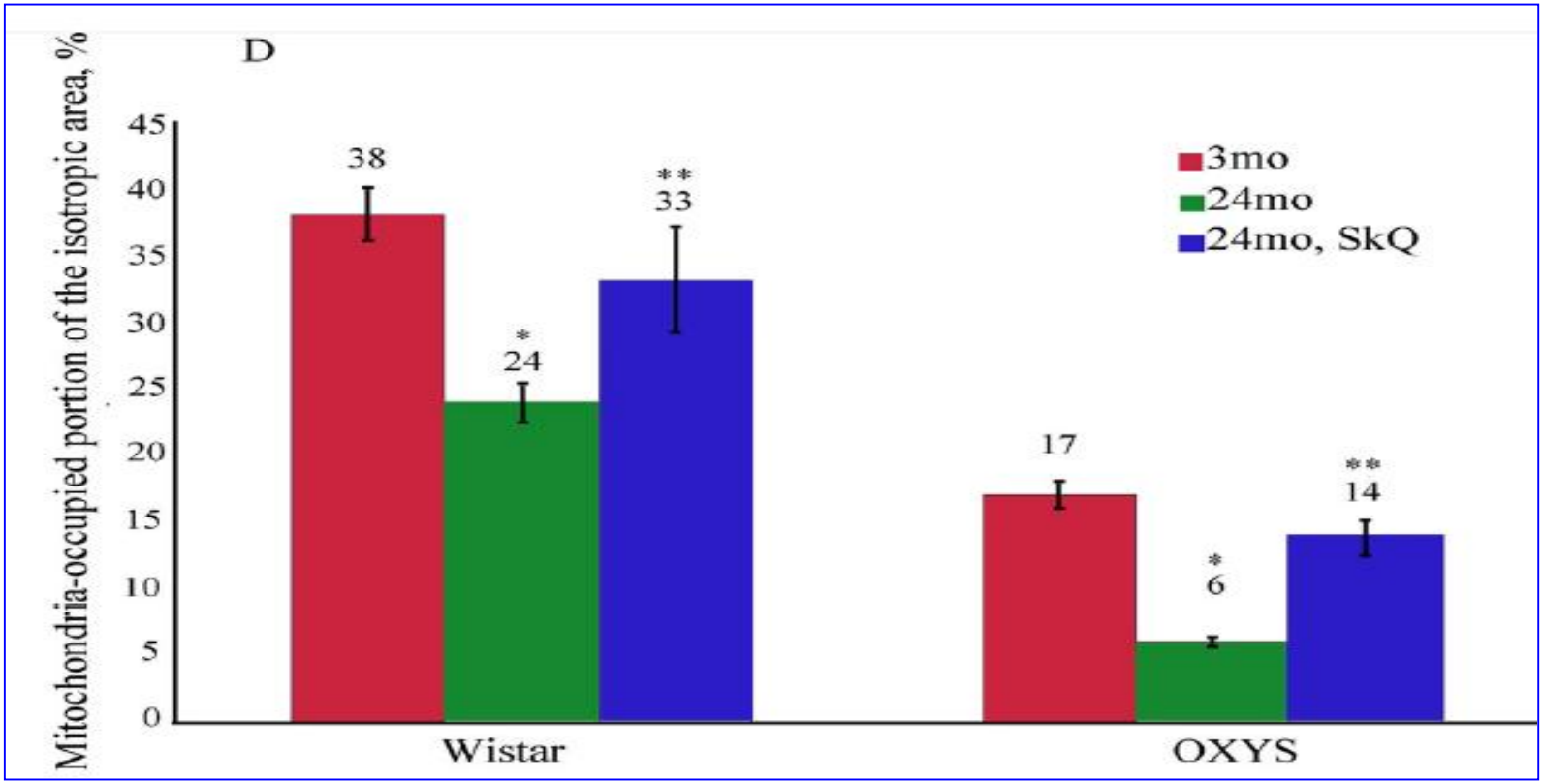


conclusion The increased levels of endogenous antioxidant enzymes after Vitamin E and C supplementation appear to be regulated by post-transcriptional modifications that are affected differently by age, exercise, and supplementation. These data suggest that antioxidant supplementation improves indices of oxidative stress associated with repetitive loading exercise and aging and improve the positive work output of muscles in aged rodents.

Antioxidant SkQ1 delays sarcopenia-associated damage of mitochondrial ultrastructure

AGING, February 2014, Vol. 6 No.2

Statistic analysis of the volume occupied by the skeletal muscle mitochondria

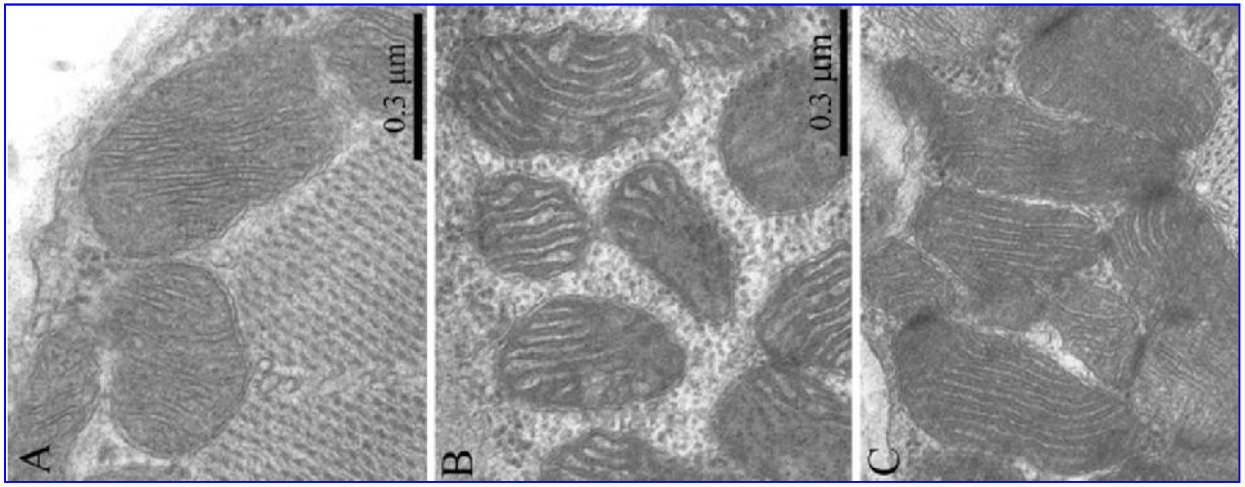


mitochondria-targeted antioxidant SkQ1[10-(6'-plastoquinonyl) decyltriphenylphosphonium]

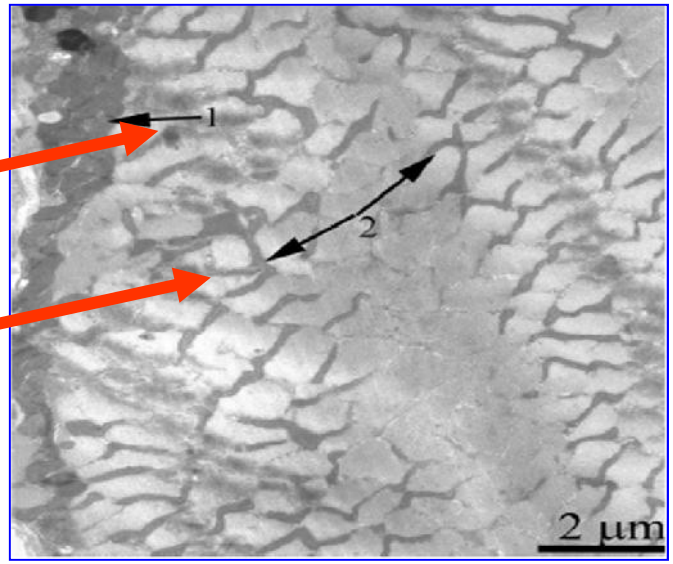
Antioxidant SkQ1 delays sarcopenia-associated damage of mitochondrial ultrastructure

AGING, February 2014, Vol. 6 No.2

3 mo. **24mo** **24mo. with SkQ1**

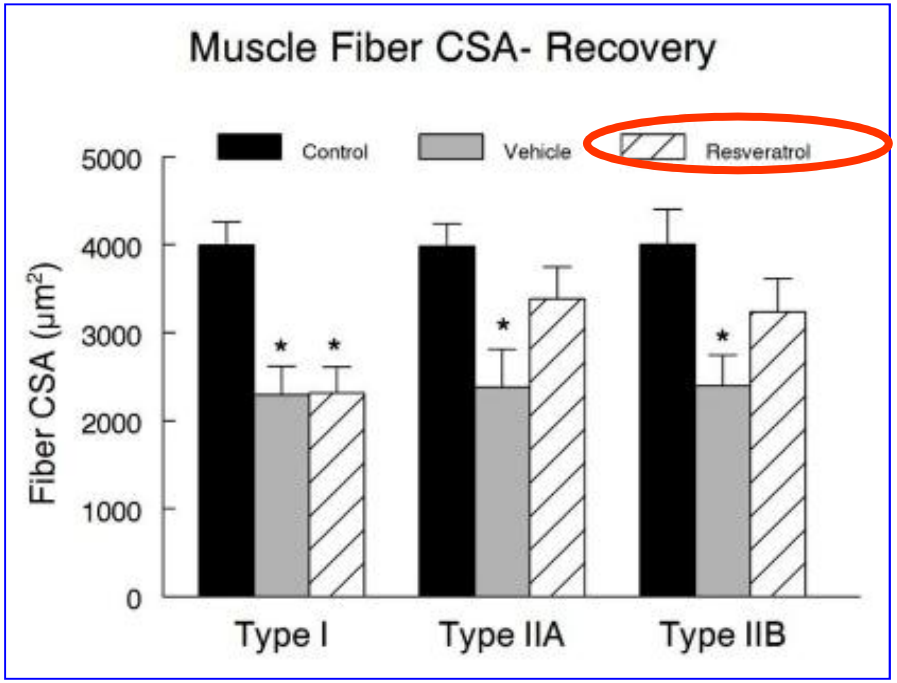


A fragment of the muscle fiber from a 24-month-old Wistar rat treated with SkQ1.
Subsarcolemmal population
of mitochondria (1)
interfibrillar stretched mitochondria (2).

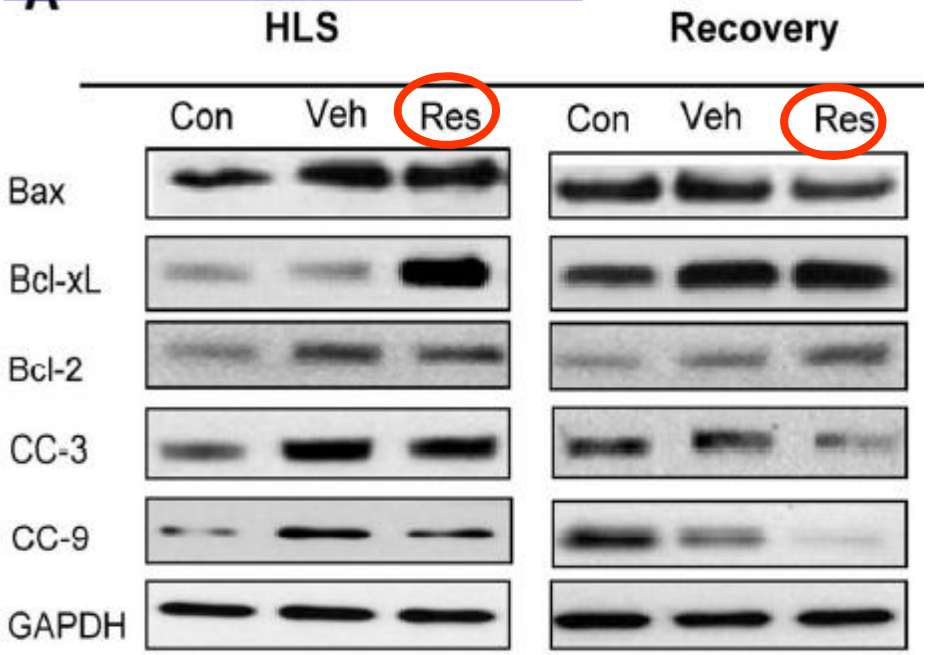


Effects of Resveratrol on the Recovery of Muscle Mass Following Disuse in the Plantaris Muscle of Aged Rats

PlosOne, 2013



APOPTOTIC SIGNALLING

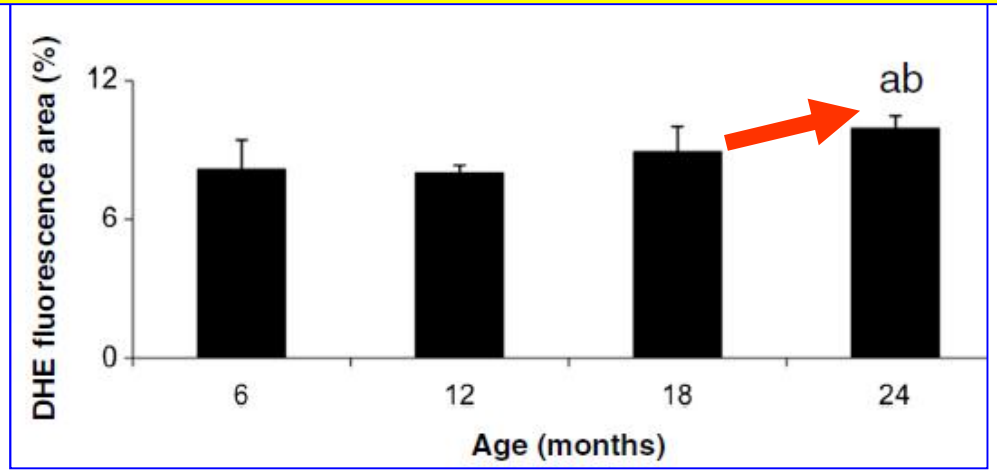


The data show that resveratrol supplementation improved muscle mass during reloading after hindlimb suspension. Although resveratrol did not prevent fiber atrophy during the period of disuse, it increased the fiber cross sectional area of type IIA and IIB fibers in response to reloading.

Elevated hydrogen peroxide and decreased catalase and glutathione peroxidase protection are associated with aging sarcopenia

BMC Geriatrics 2013, **13**:104

$O2^-$ levels in aging skeletal muscle, by histological DHE examination



Enzyme activity and hydrogen peroxide levels in aging skeletal muscle

	Age (months)				
	6 ($n = 16$)	12 ($n = 18$)	18 ($n = 12$)	24 ($n = 12$)	Gene expres
SOD1 (U/mg protein)	19.4 ± 1.3	9.1 ± 0.3^{acd}	30.8 ± 2.5^{abd}	25.9 ± 1.3	+++
SOD2 (U/mg protein)	5.7 ± 0.5	5.7 ± 0.4	4.7 ± 0.3	3.4 ± 0.1^{ab}	+
GPx (U/mg protein)	1.0 ± 0.2	1.1 ± 0.1^{a}	0.7 ± 0.1^{abd}	0.9 ± 0.2	++
Catalase (U/mg protein)	9.3 ± 0.9	12.1 ± 1.2^{a}	8.8 ± 1.2^{bd}	10.2 ± 0.9	++
Hydrogen Peroxide (μM)	1.12 ± 0.07	1.16 ± 0.04	2.42 ± 0.05^{abd}	1.74 ± 0.06	
Superoxide (AFU)	8.1 ± 1.3	8.0 ± 0.3	8.9 ± 1.1	10.0 ± 0.6^{ab}	

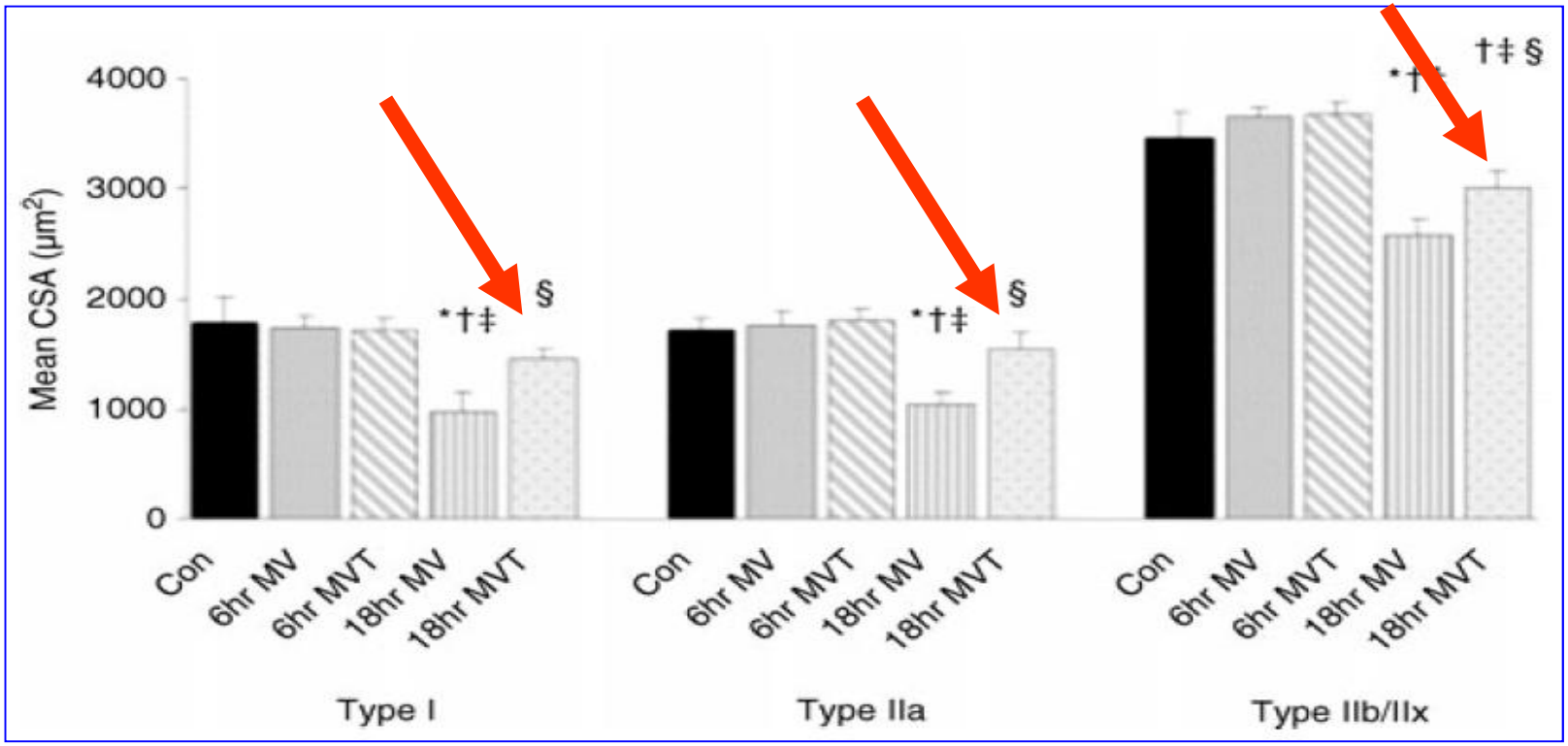
SYMPOSIUM REVIEW

Pellegrino M et al.

Redox homeostasis, oxidative stress and disuse muscle atrophy

J Physiol 589.9 (2011) pp 2147–2160

The impact of mechanical ventilation and antioxidant administration (Trolox) on cross-sectional areas (CSA) of different muscle fibres (type I, IIa and IIb/x)



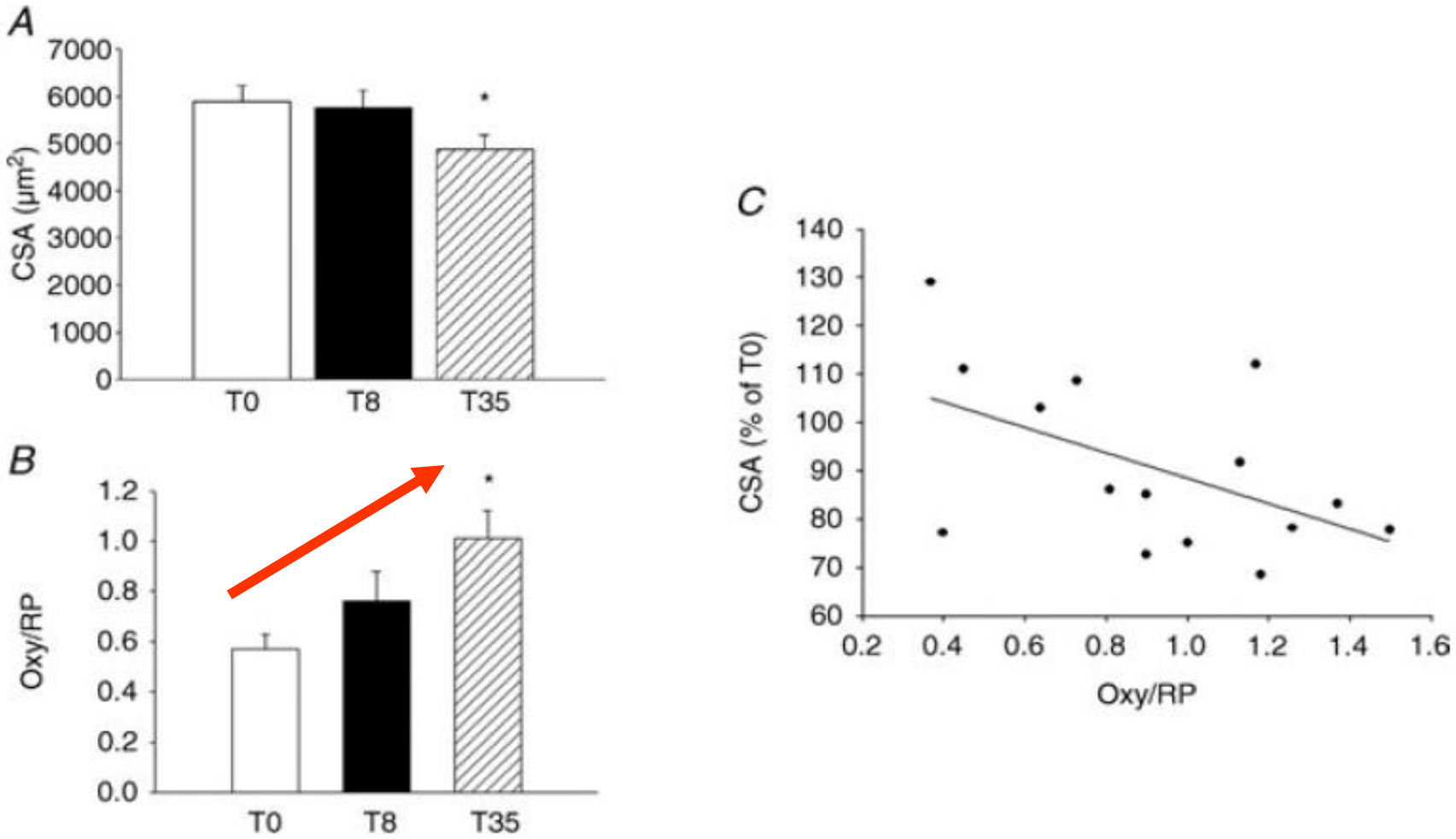
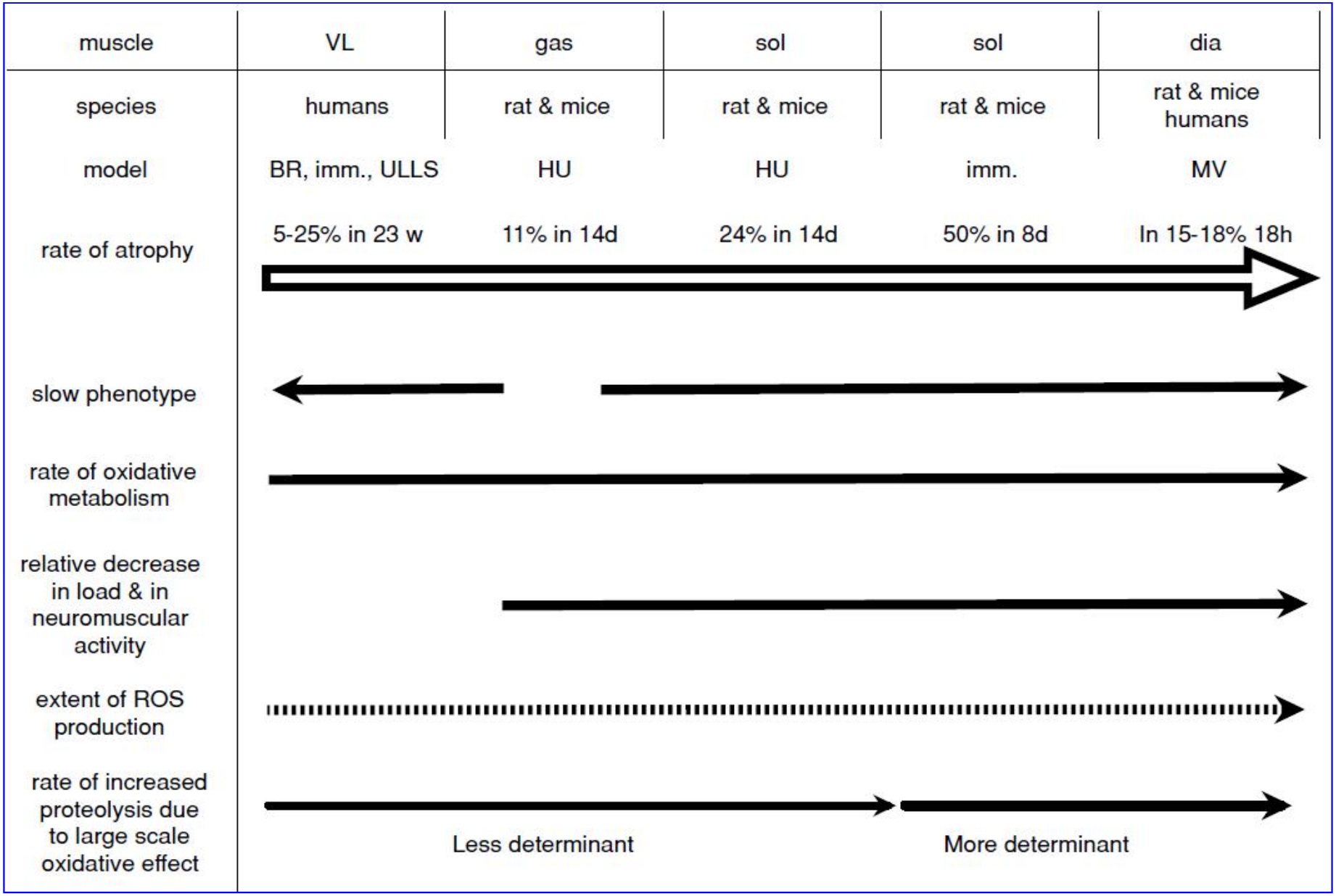


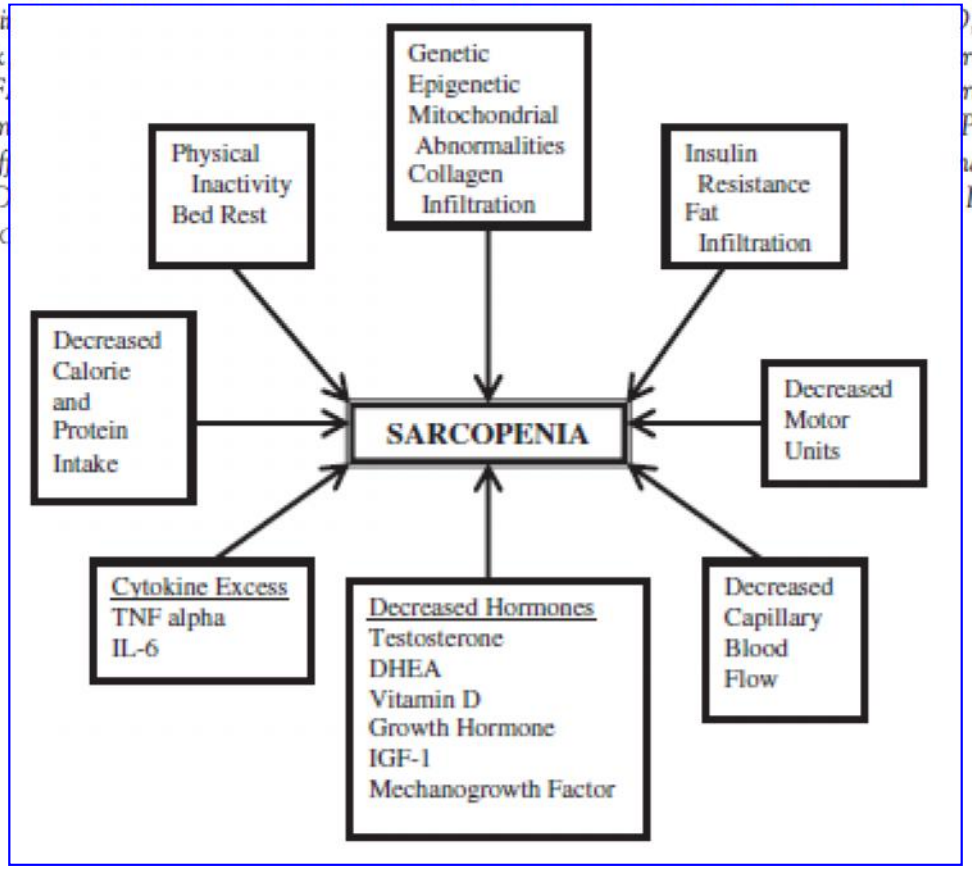
Figure 4. The impact of 8 (T8) and 35 (T35) days of bed rest on cross-sectional area (CSA) of muscle fibres and on protein oxidation (Oxy/RP) of muscle samples from the vastus lateralis muscle of humans
A, mean values of CSA of muscle fibres before bed rest (T0) and at T8 and T35. *B*, protein oxidation index (Oxy/RP). *Significantly different from T0 ($P < 0.05$). *C*, regression analysis of normalized values of muscle protein oxidation (Oxy/RP) plotted against the percentage change of fibre CSA of the same muscles, determined at T8 and T35; the slope of the line was significantly different from zero ($P < 0.05$), reprinted from Dalla Libera *et al* 2009 used with permission from The American Physiological Society.

Alterations of redox homeostasis through muscles, species and models



Sarcopenia With Limited Mobility: An International Consensus

John E. Morley, MB, BCh, Angela Marie Abbatecola, BS, MD, PhD, Josep M. Argiles, PhD, Vickie Baracos, BSc, PhD, Juergen Bauer, MD, PhD, Shalender Bhasin, MD, Tommy Cederholm, MD, PhD, Andrew J. Stewart Coats, DM, DSc, Steven R. Cummi, Roger A. Fielding, PhD, Jack M. Guralnik, r-Zadeh, MD, PhD, MPH, FAAP, FACP, F, rizio Muscaritoli, MD, Anne B. Neuman, PhD, FESC, Ronenn Roubenoff, as W. Storer, PhD, Bruno Vellas, MD, D. Anker, MD, PhD, THE SOCIETY ON SARC

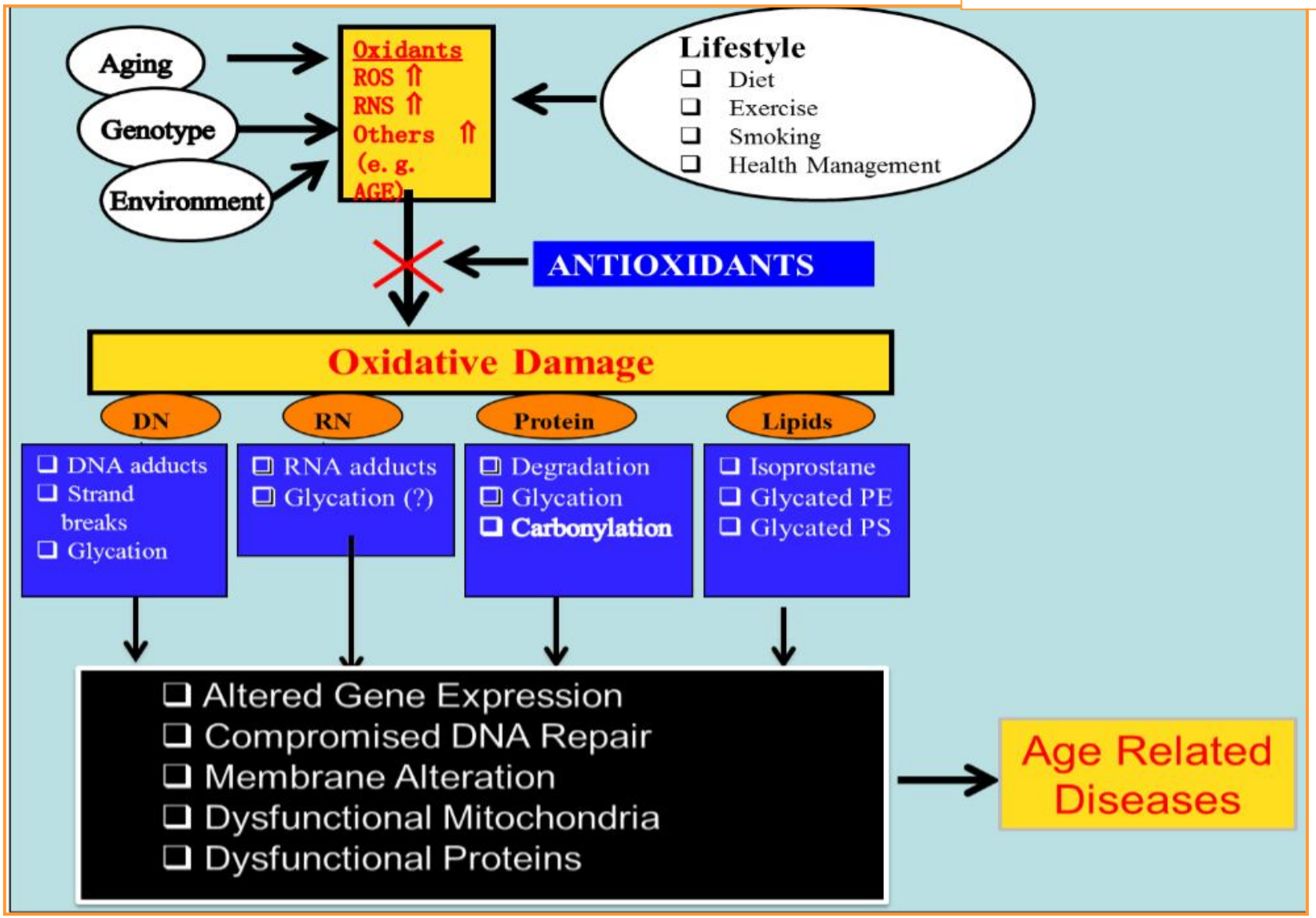


2011; 12: 403–409

Lifestyle and Advanced Glycation End Products (AGEs) Burden: Its Relevance to Healthy Aging

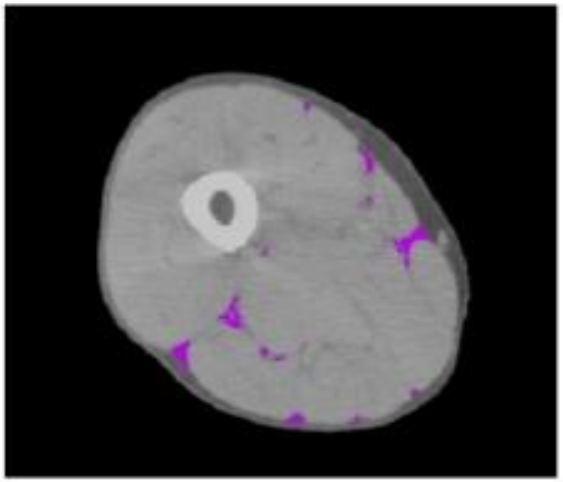
Chandan Prasad[1*], Victorine Imrhan[1], Francesco Marotta[2], Shanil Juma[1] and Parakat Vijayagopal[1]

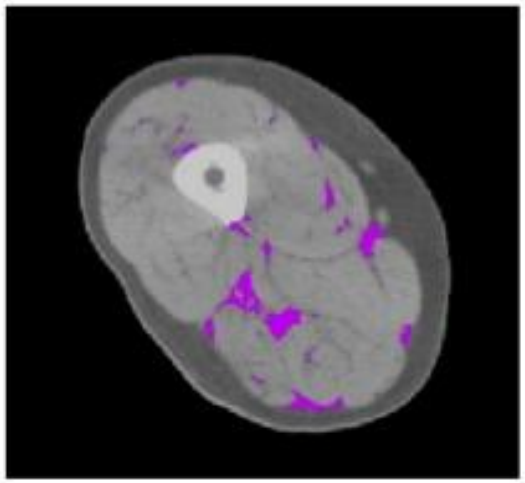
Aging & Disease, June 2014

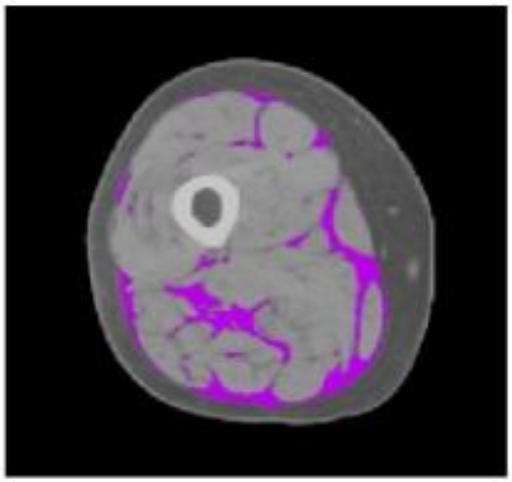


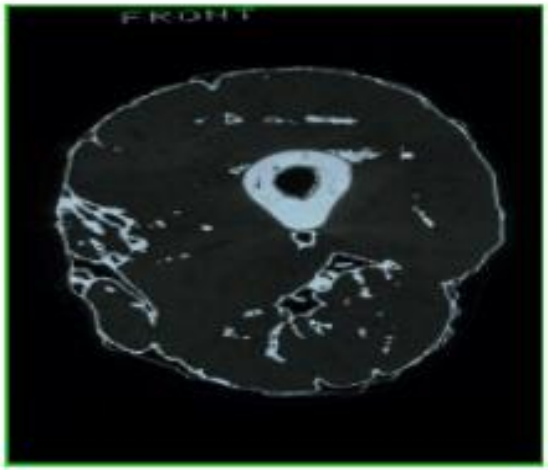
With Sarcopenic Obesity increases in

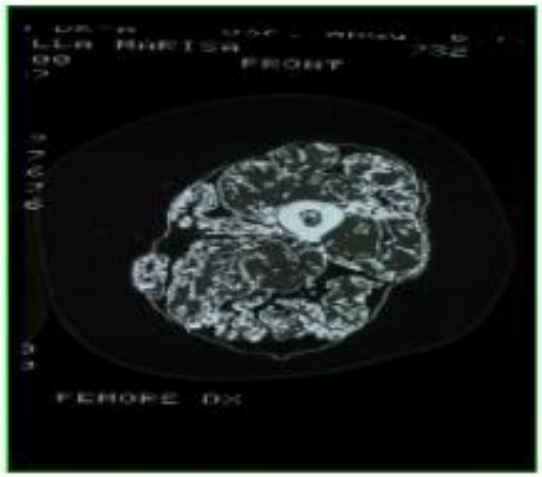
Intermuscular Fat





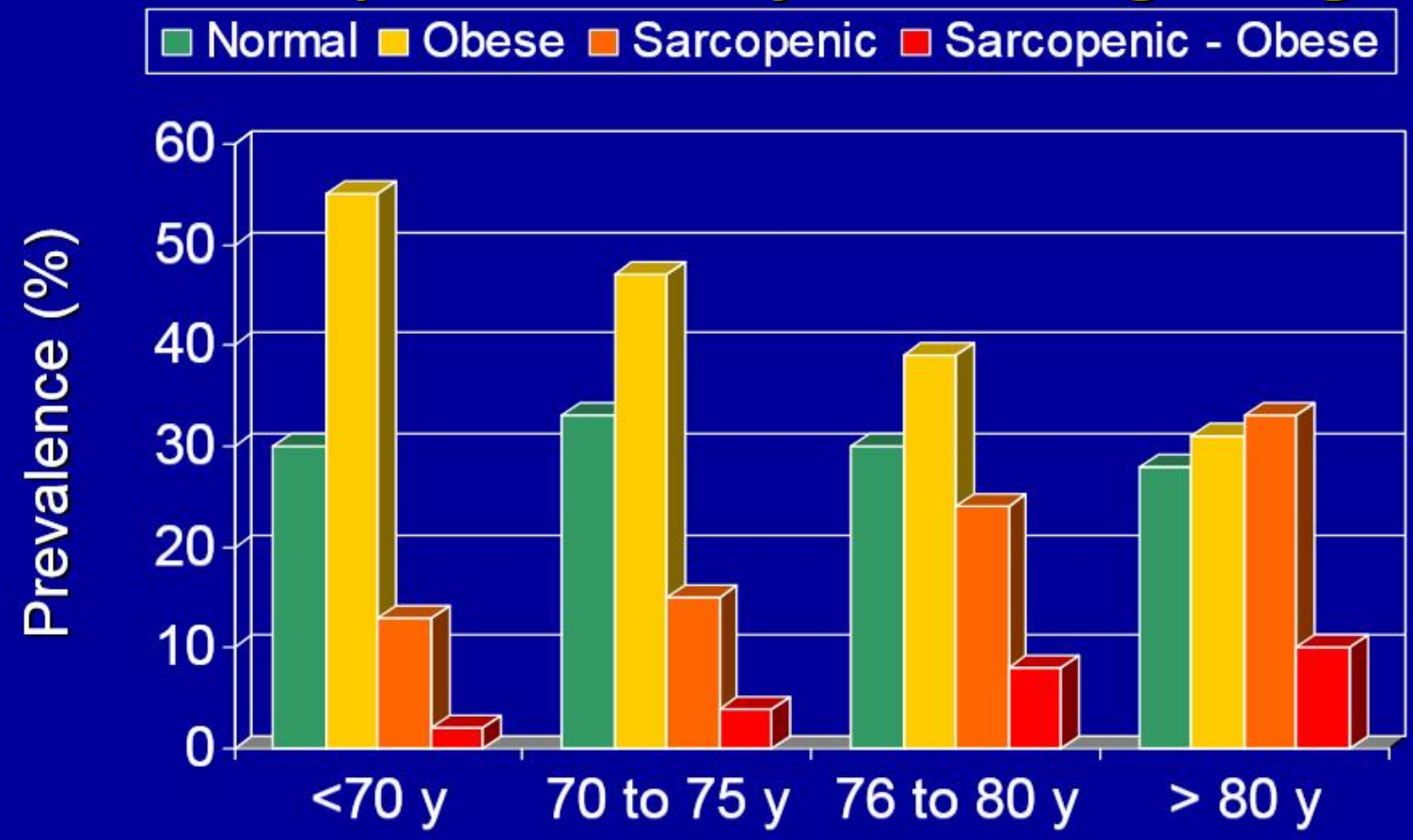






and Intramuscular fat: Low Density Lean Tissue by CT

Prevalence of obesity, sarcopenia, and sarcopenic-obesity according to age



Baumgartner RN Ann NY Acad Sci 2000;904:437-448