

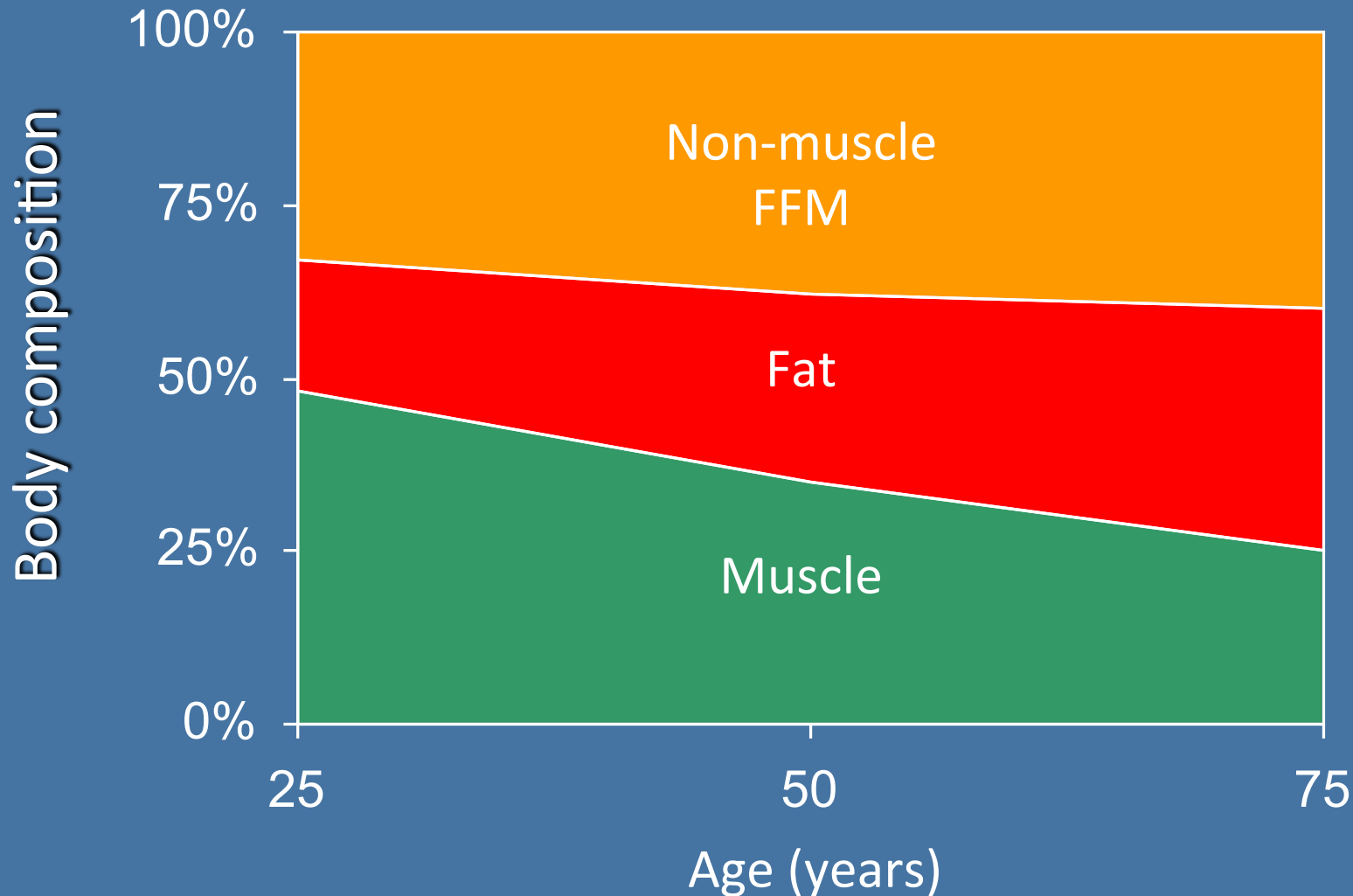


Oxidative stress, antioxidant intervention and sarcopenia

Francesco Marotta, MD, PhD (Japan)

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ReGenera Research Group for Aging Intervention, Italy

Body composition changes and aging

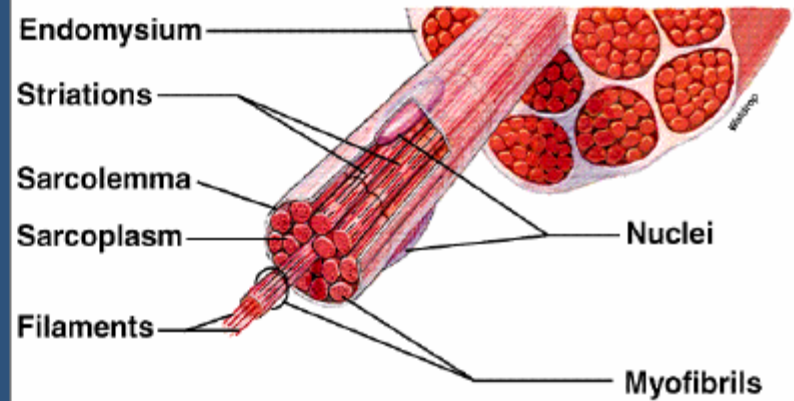




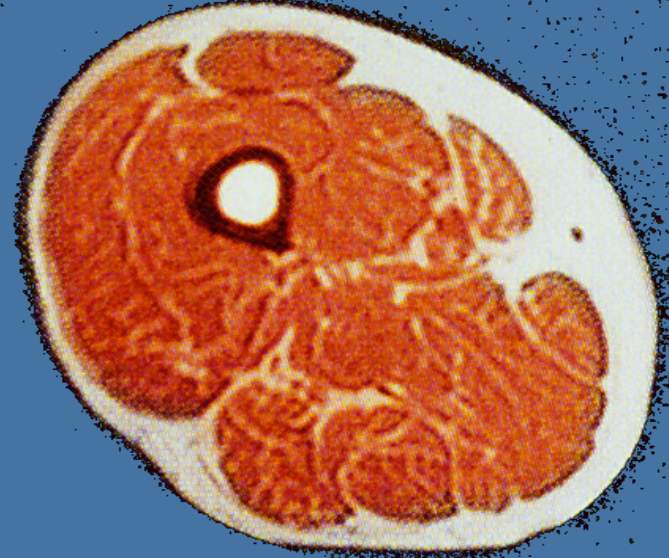
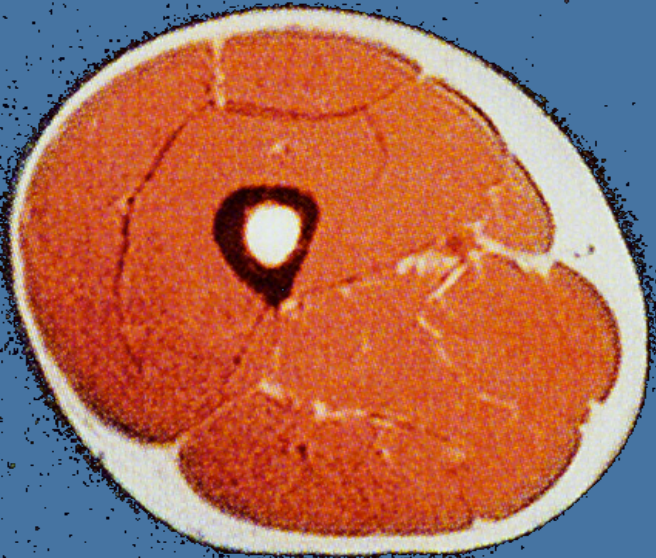
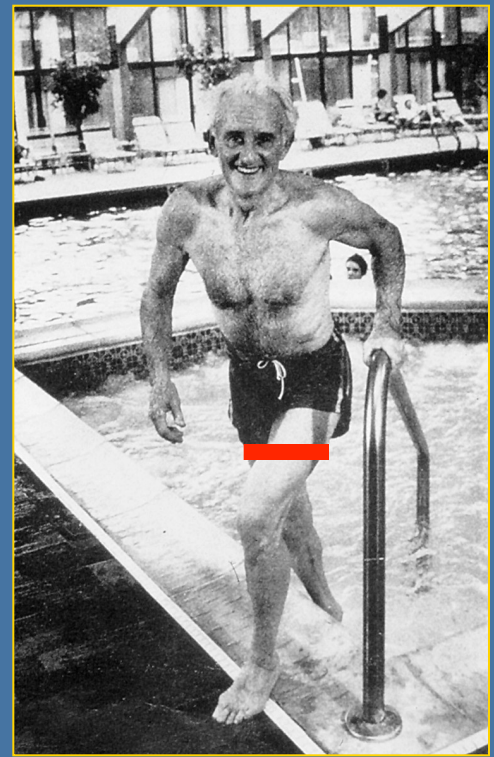
Age

Stuart I. Fox, Human Physiology, 6e. Copyright © 1999 The McGraw-Hill Companies, Inc. All rights reserved.

Skeletal Muscle—Single Muscle Fiber

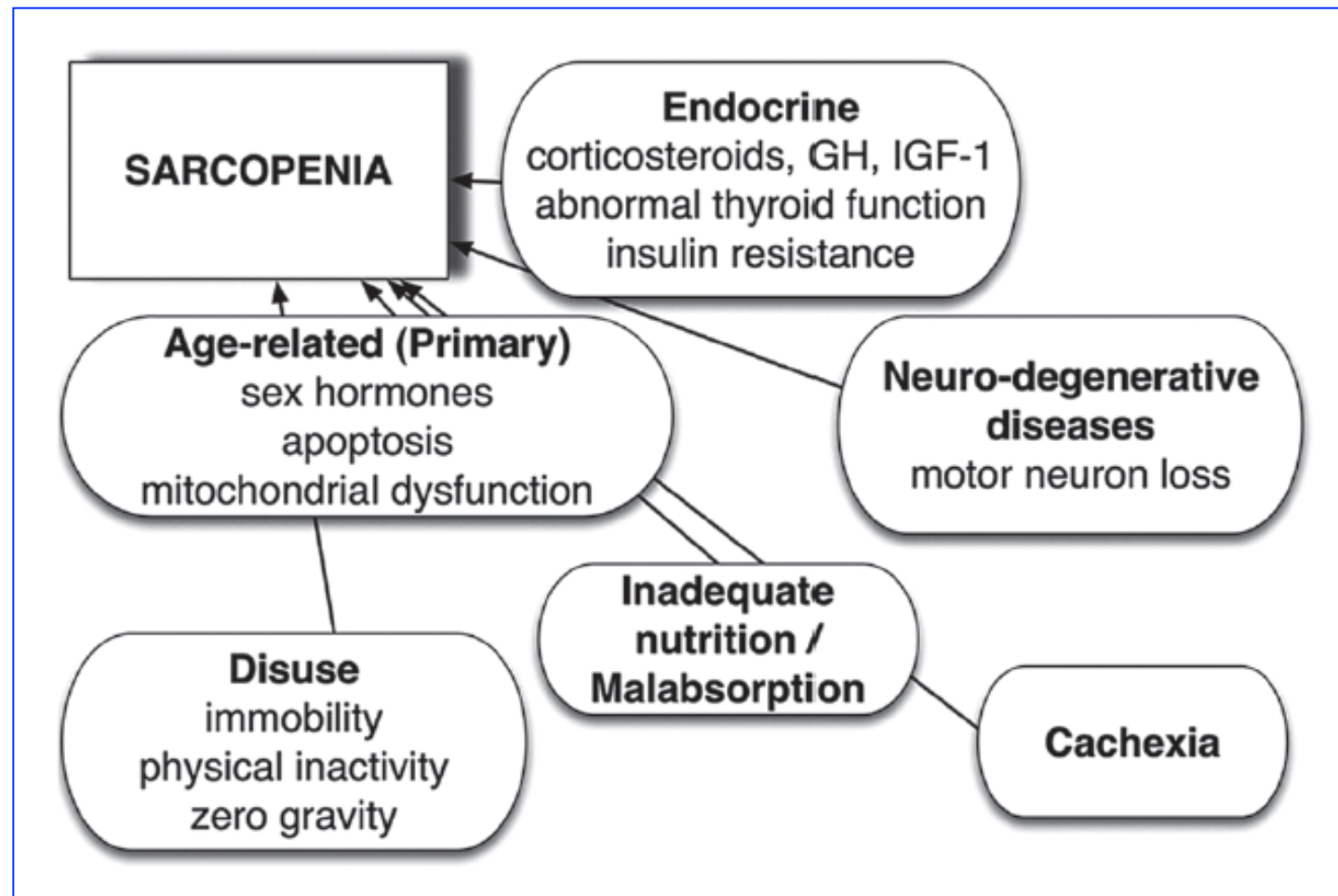


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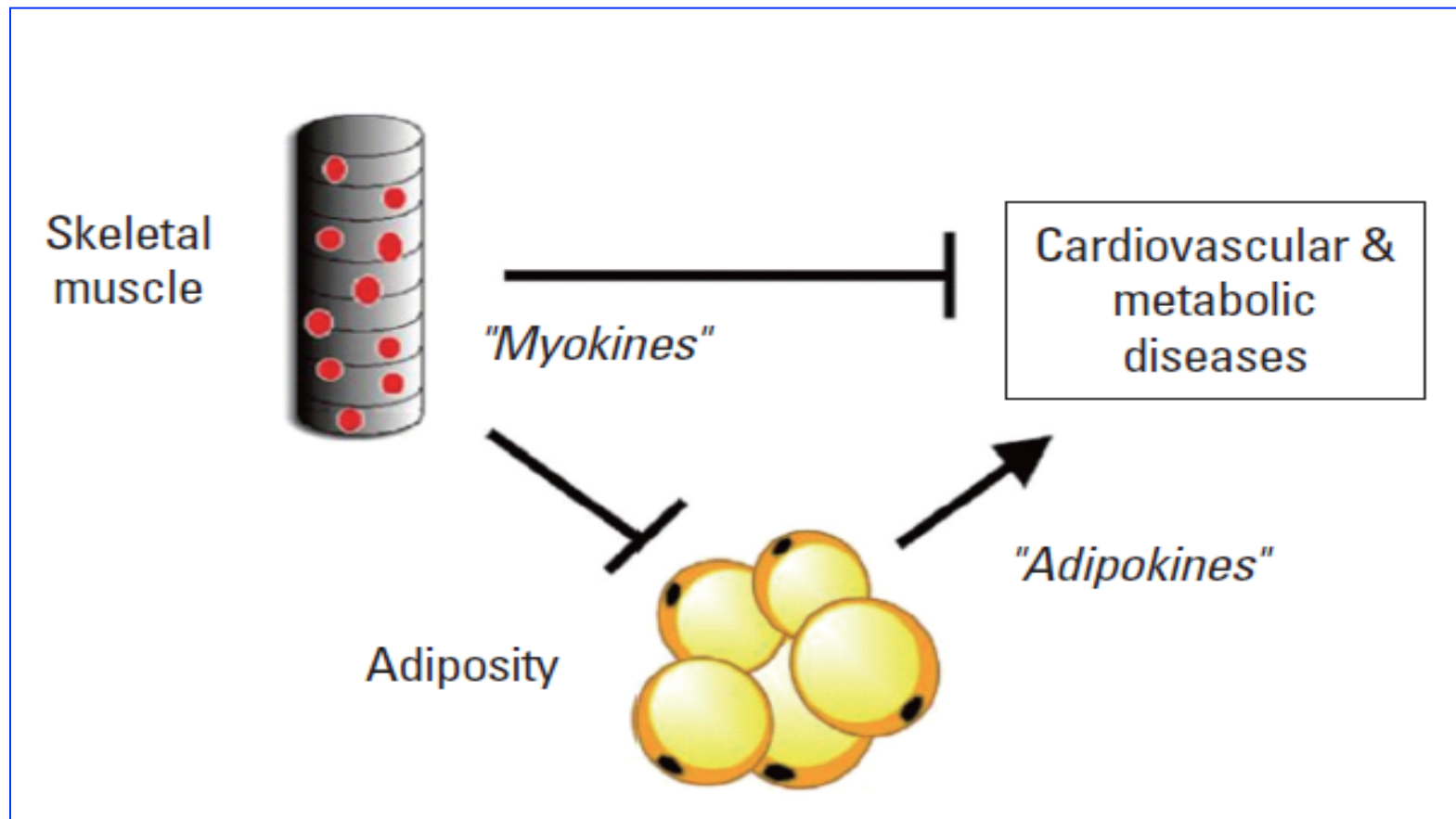
Sarcopenia: Definition, Epidemiology, and Pathophysiology

J Bone Metab 2013;20:1-10



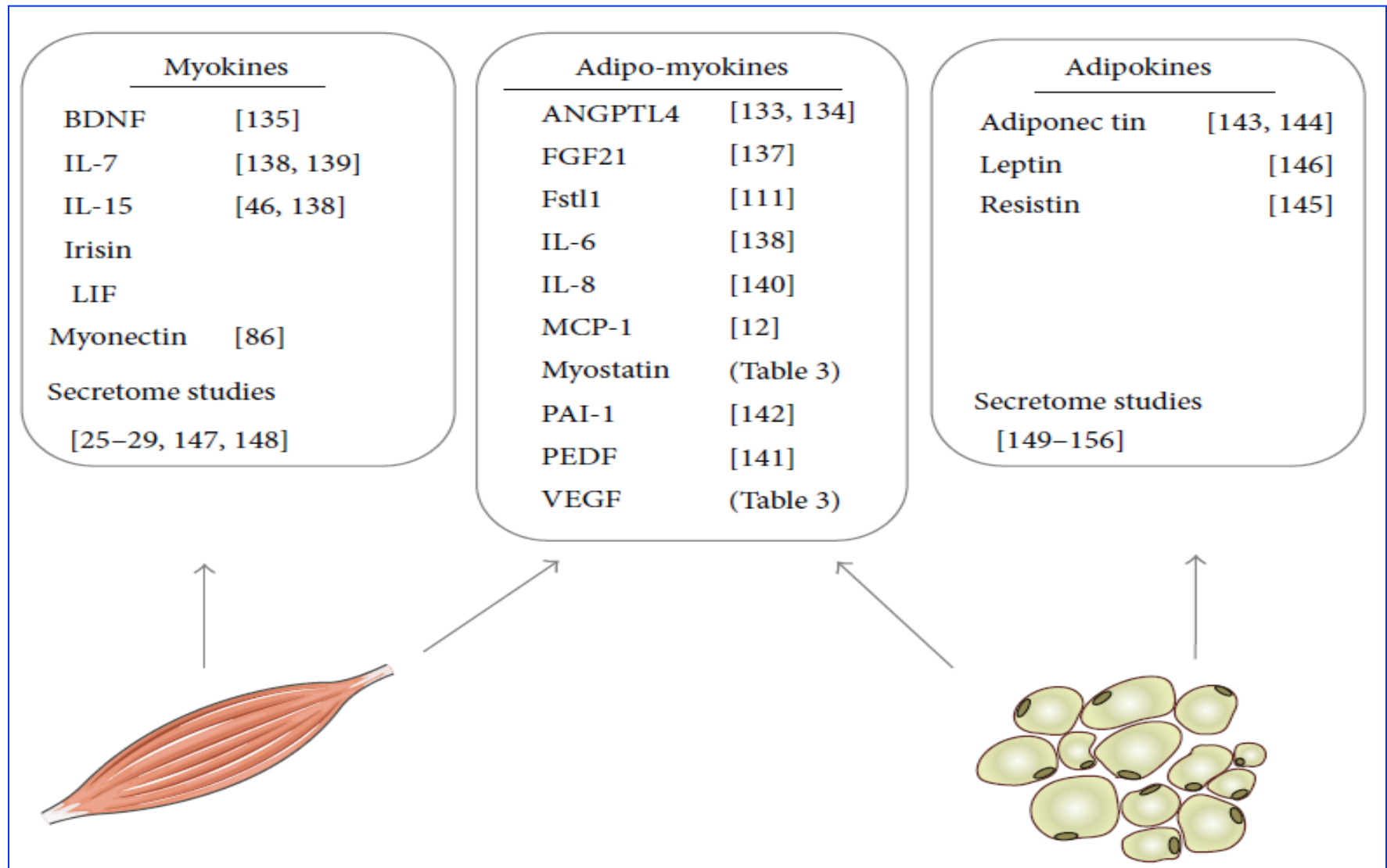
Sarcopenia: Definition, Epidemiology, and Pathophysiology

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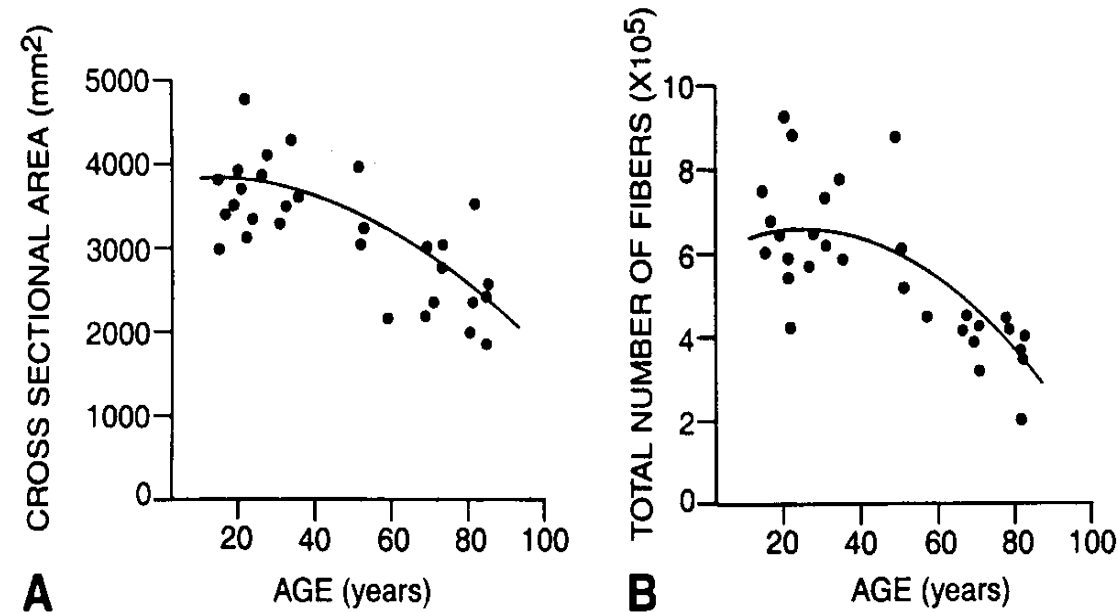
Adipo-Myokines: Two Sides of the Same Coin—Mediators of Inflammation and Mediators of Exercise

Mediators of Inflammation, 2013



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

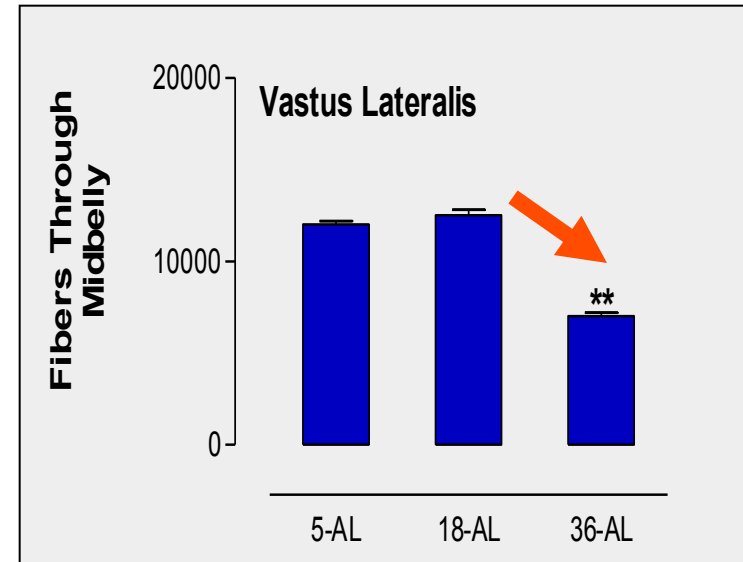
Humans



A

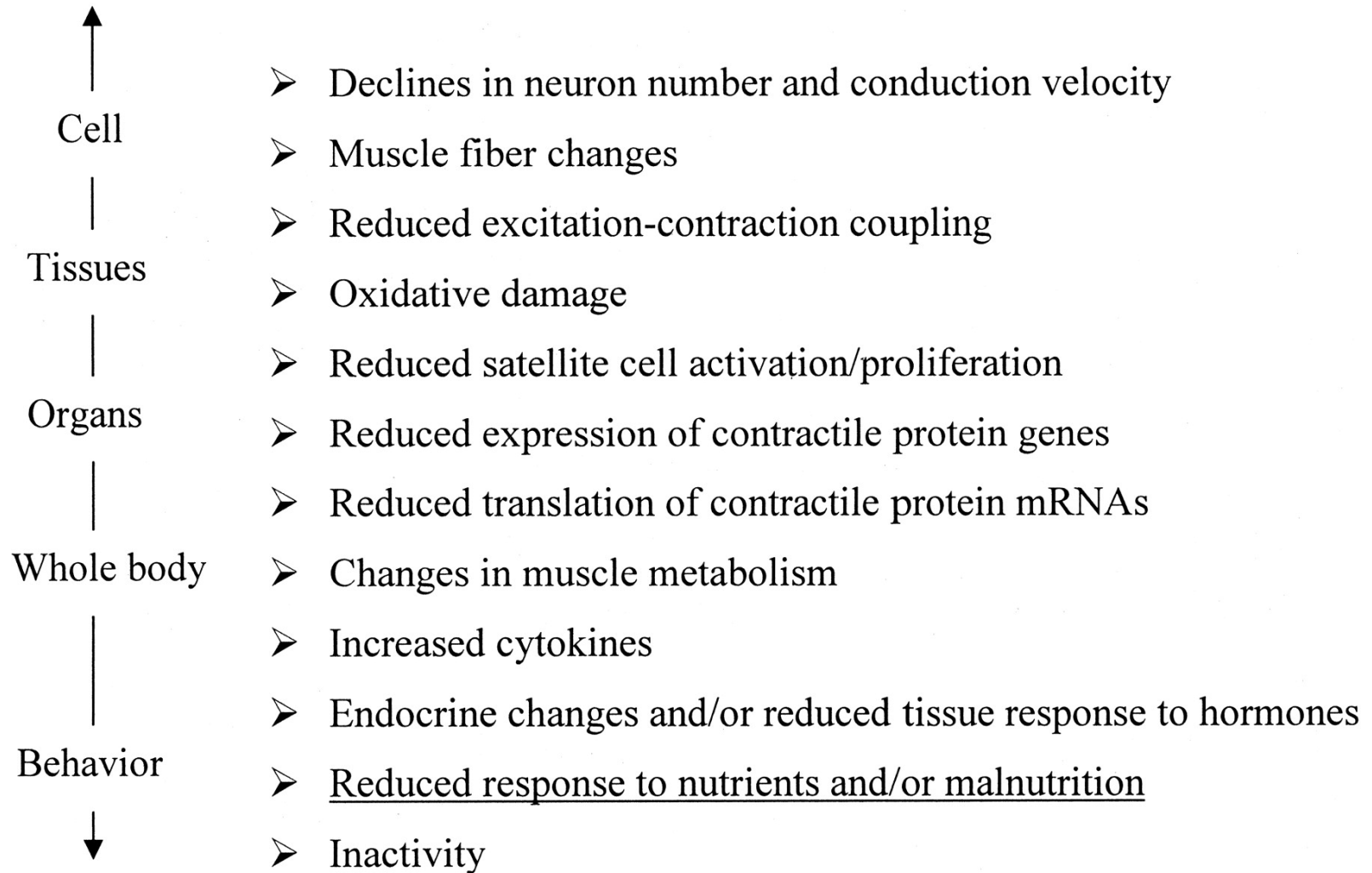
Lexell J, Taylor CC, Sjostrom M. What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. *J Neurol Sci.* 1988 Apr;84(2-3): 275-94.

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.

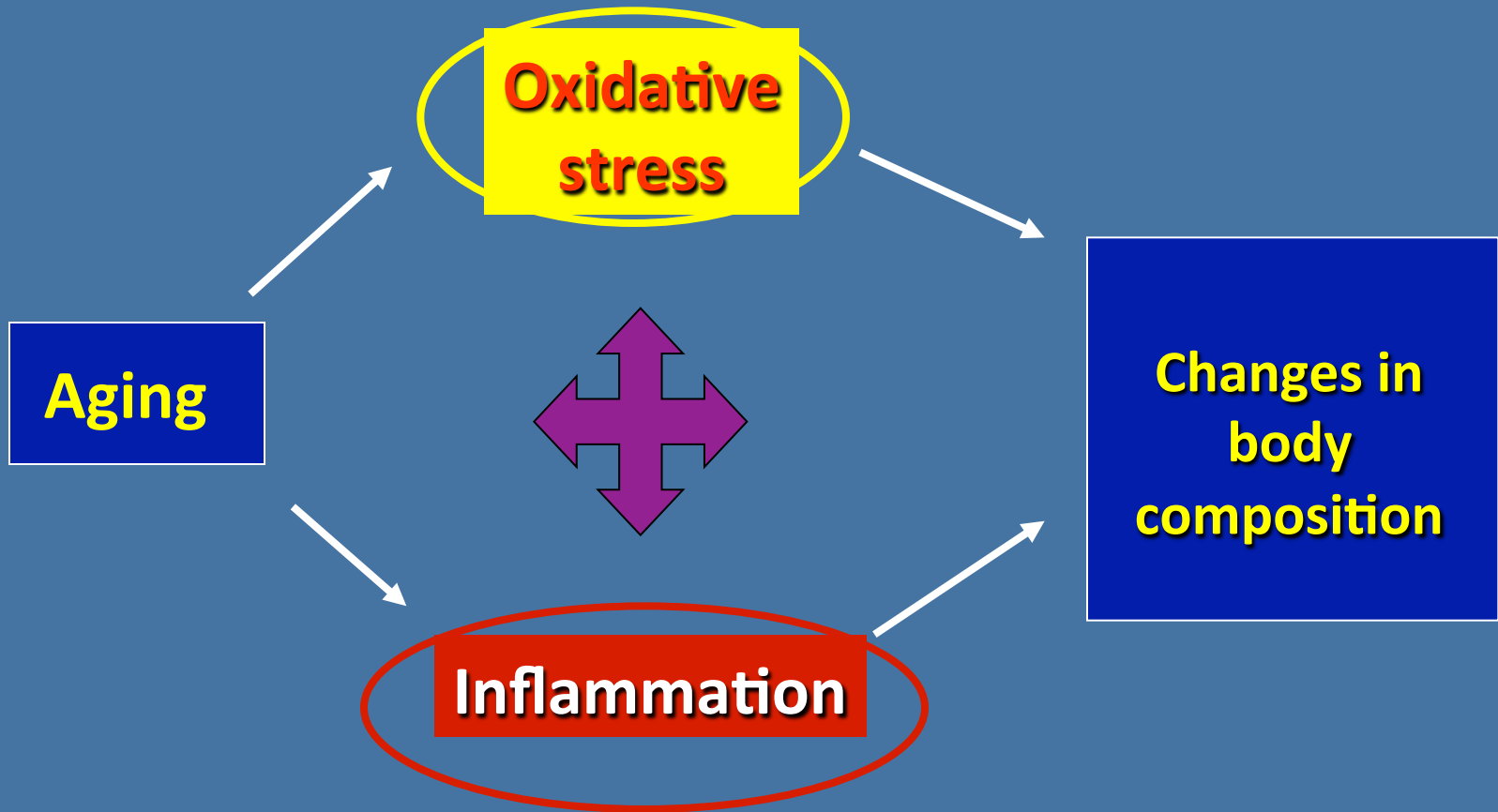
A partial list of mechanisms/consequences of sarcopenia.



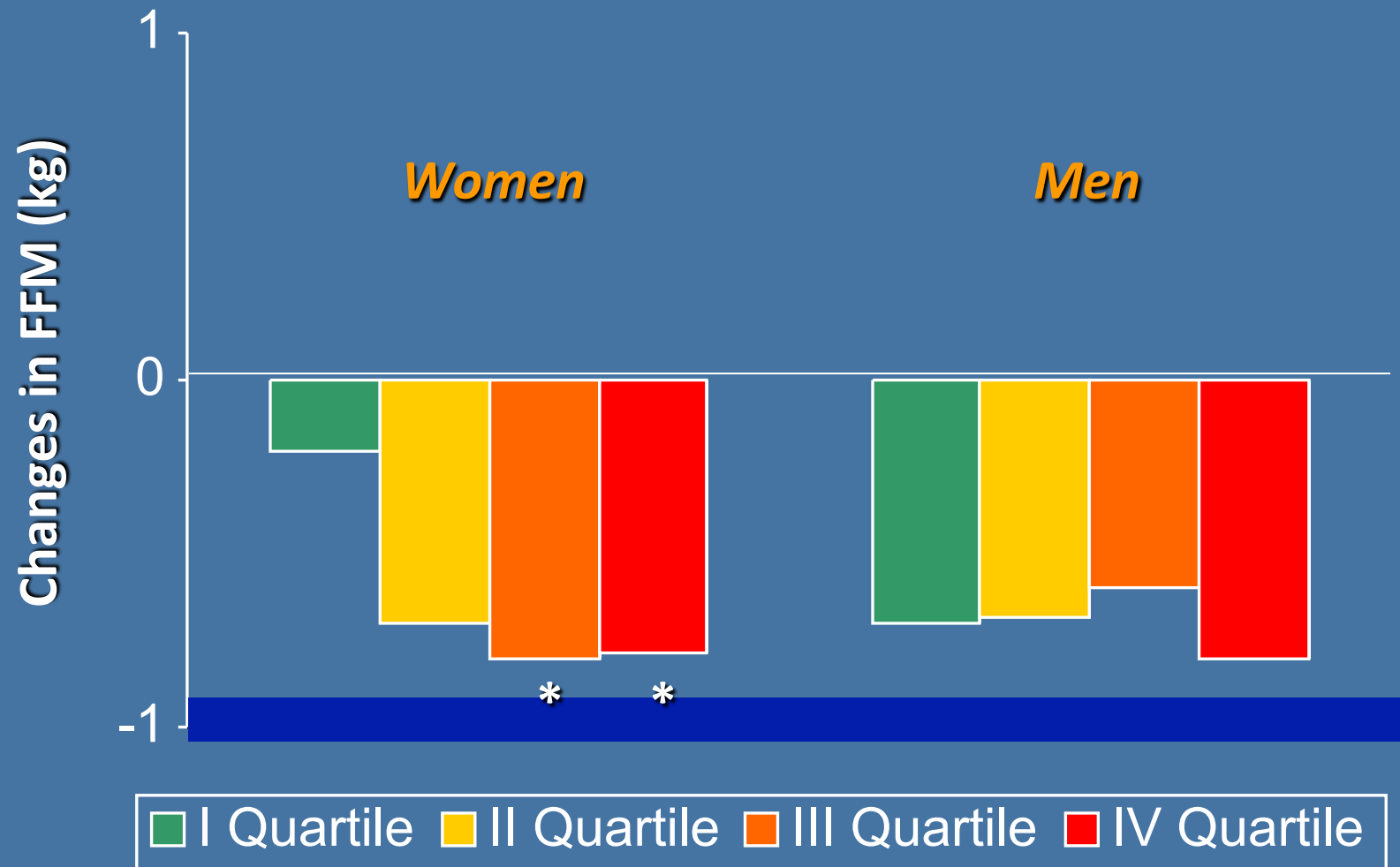
Paddon-Jones D et al. Am J Clin Nutr 2008;87:1562S-1566S



The American Journal of Clinical Nutrition



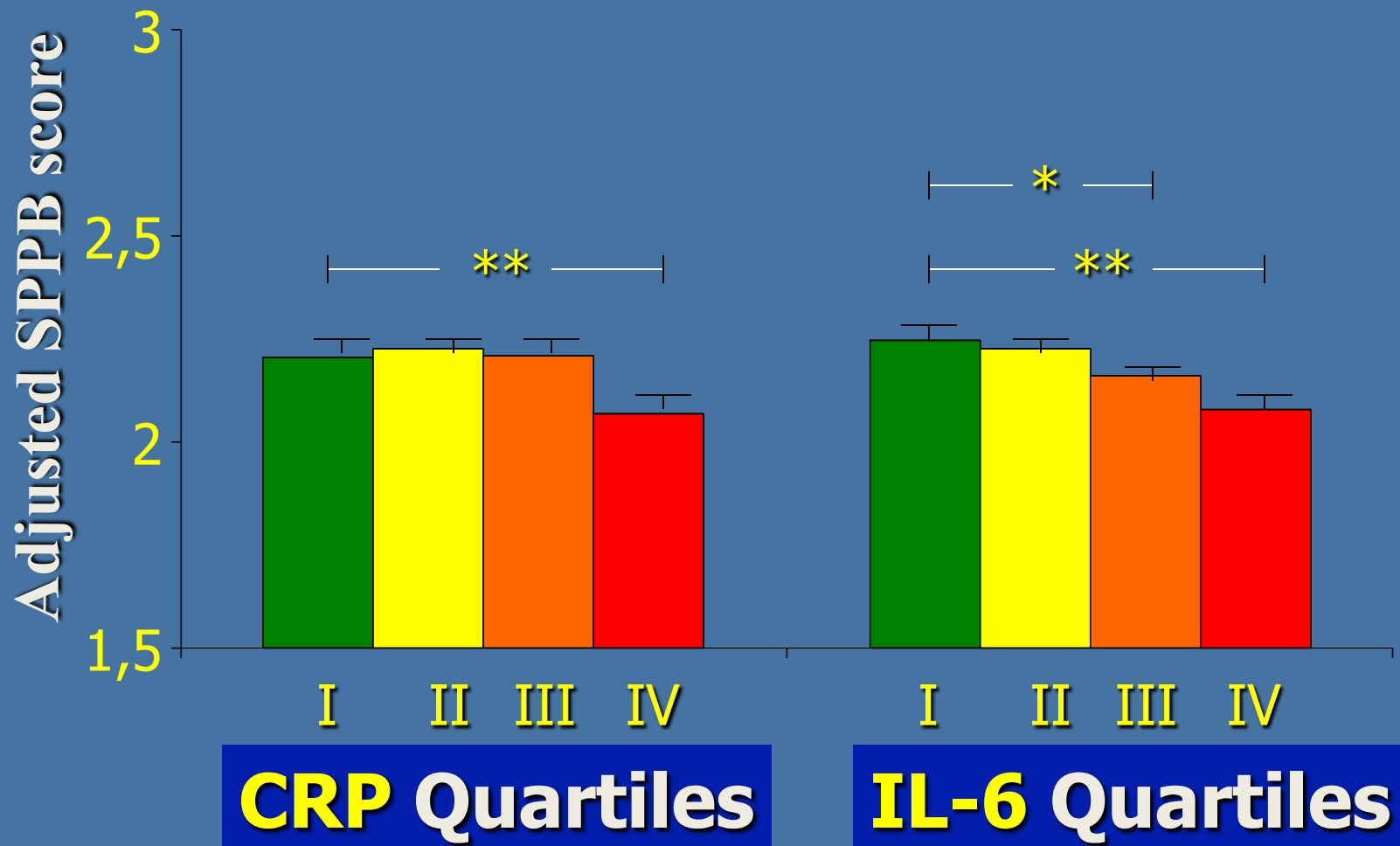
Two-year changes in fat-free mass (FFM) by IL-6 quartiles in the Framingham Heart Study



* $p < 0.05$

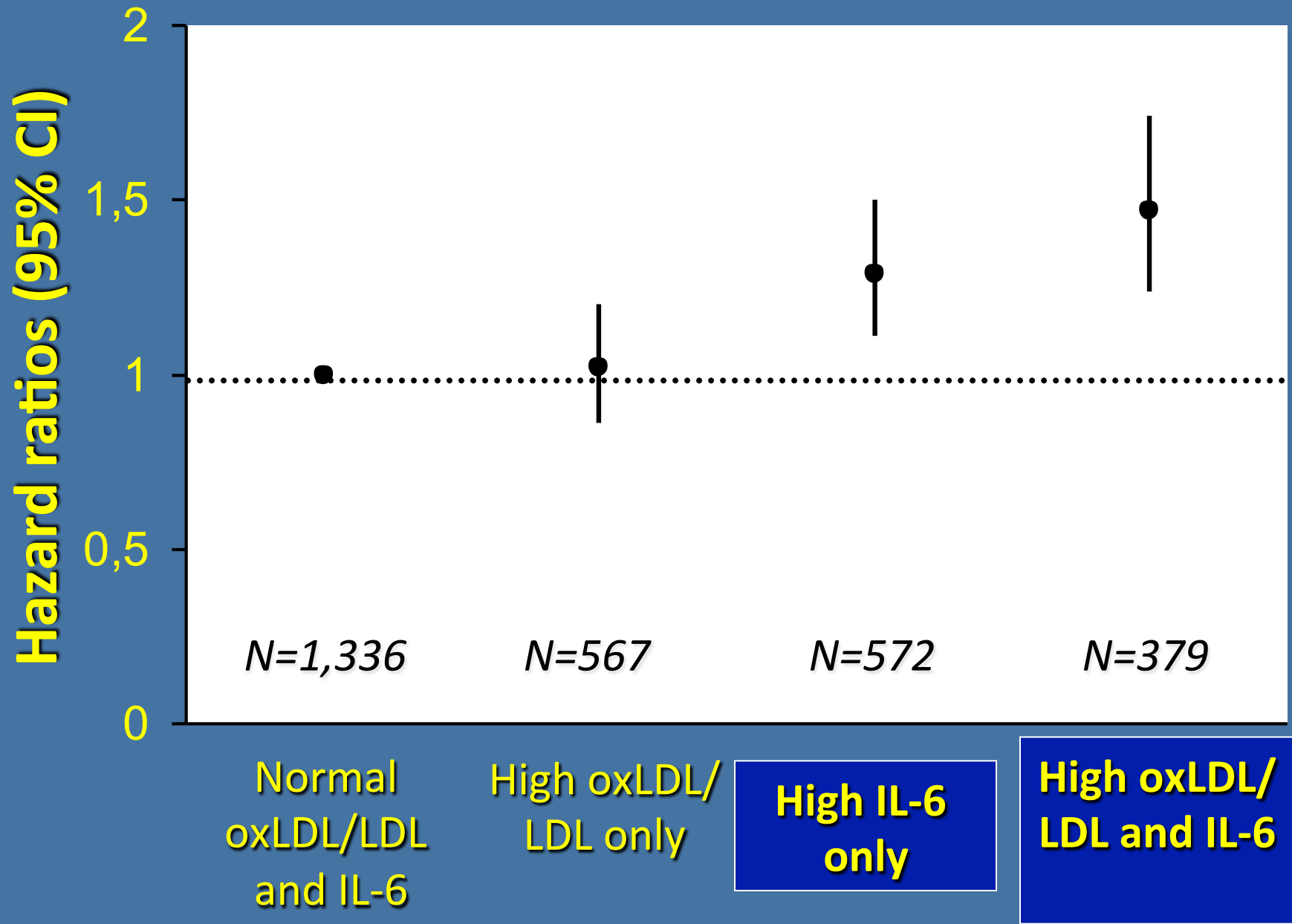
Payette H J Am Geriatr Soc 2003;51:1237-1243

Short Physical Performance Battery



Adjusted for sociodemographics, comorbidities, biological markers and medications

MOBILITY LIMITATION



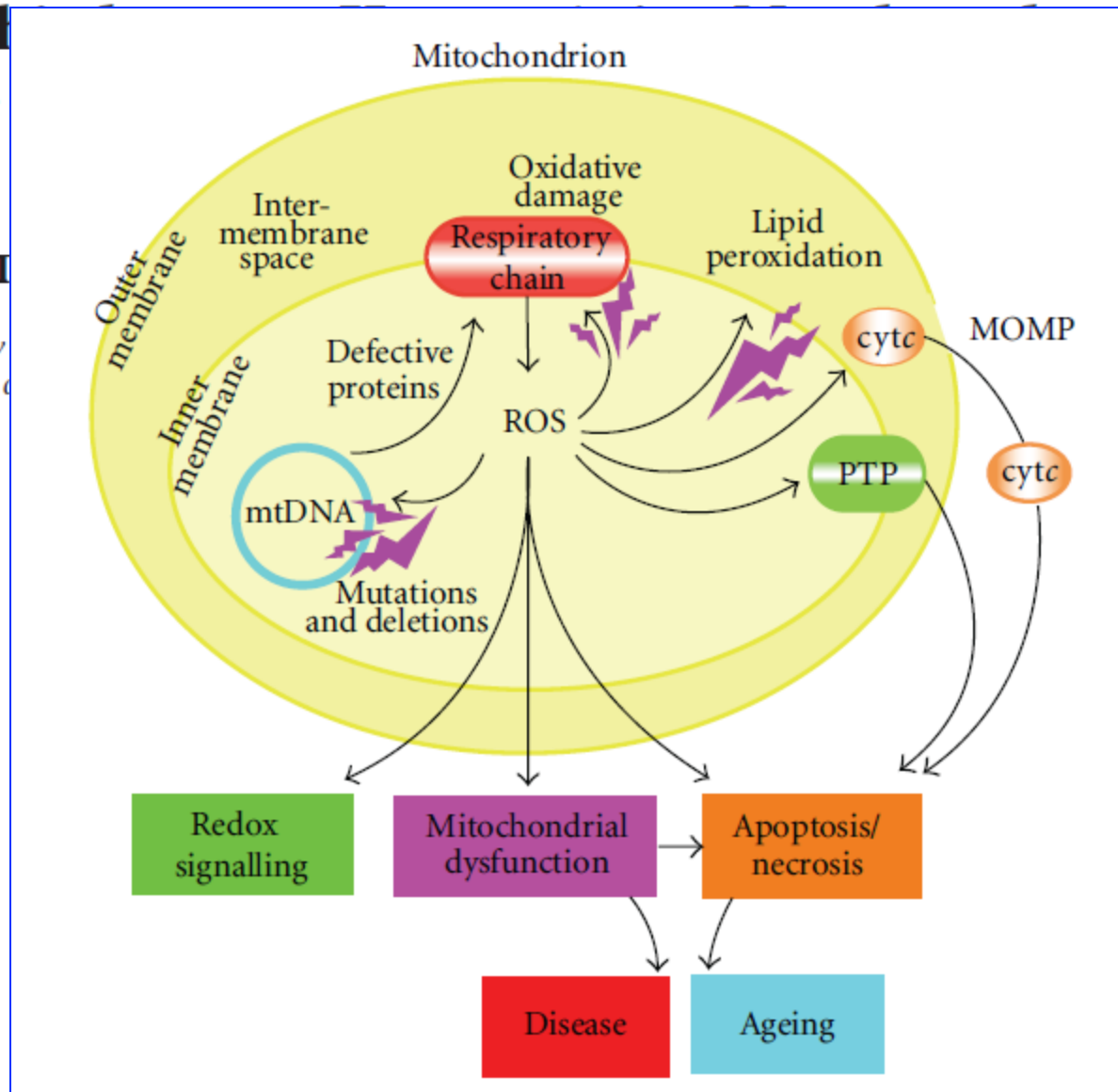
Relationships between Mitochondrial Dysfunction and Oxidative Stress

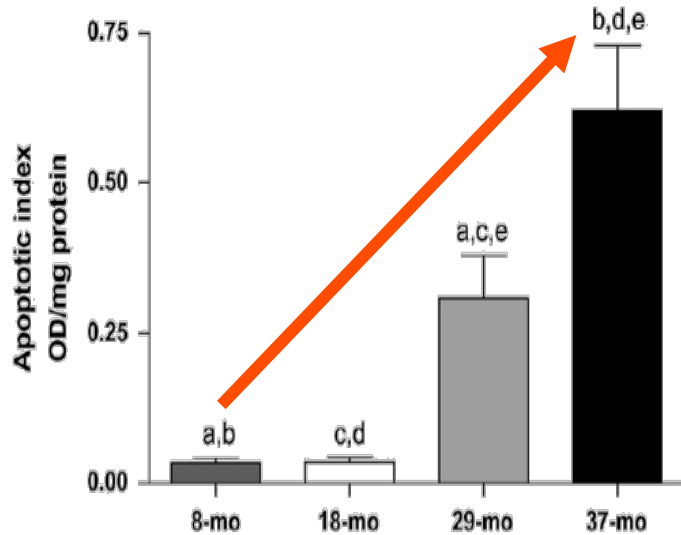
Enrico I. Cadenas

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University of Valencia

Enrico I. Cadenas

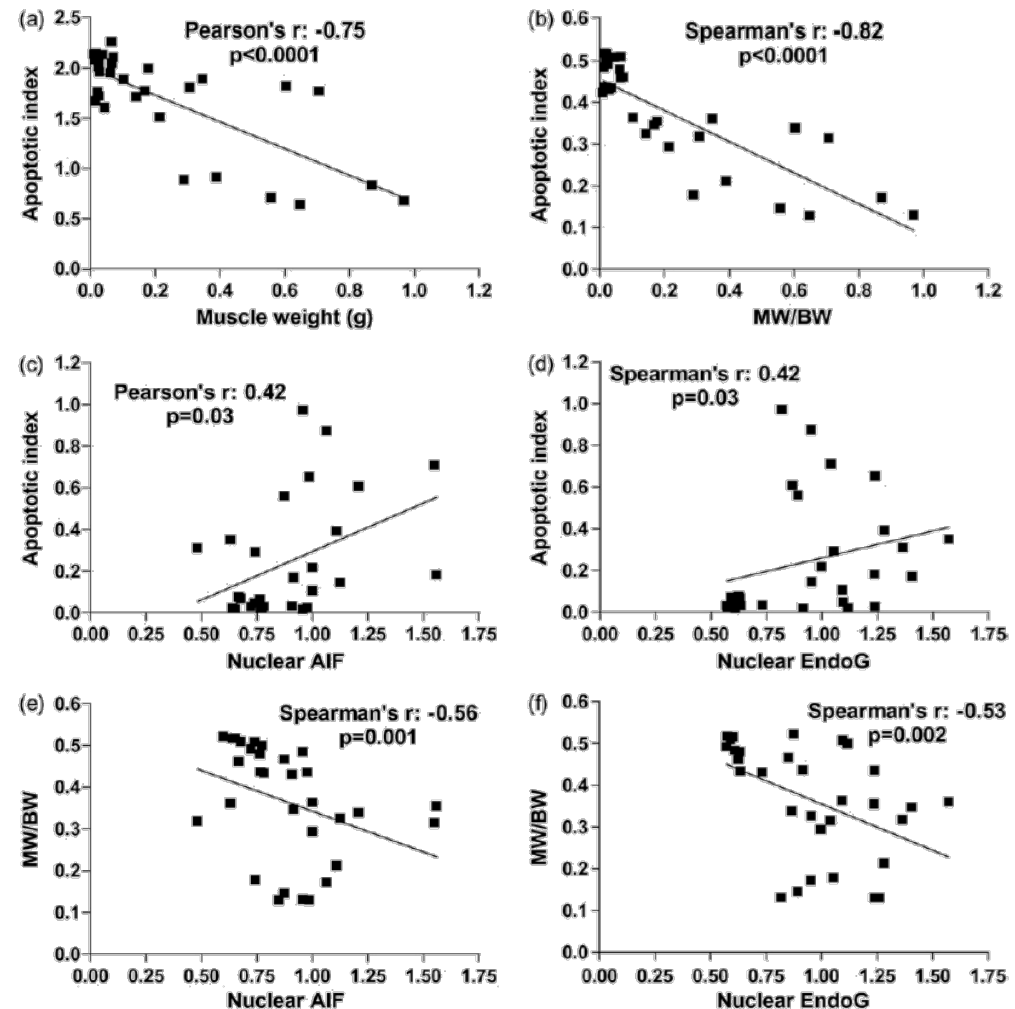
Laboratory of Mitochondrial Medicine,
University of Valencia



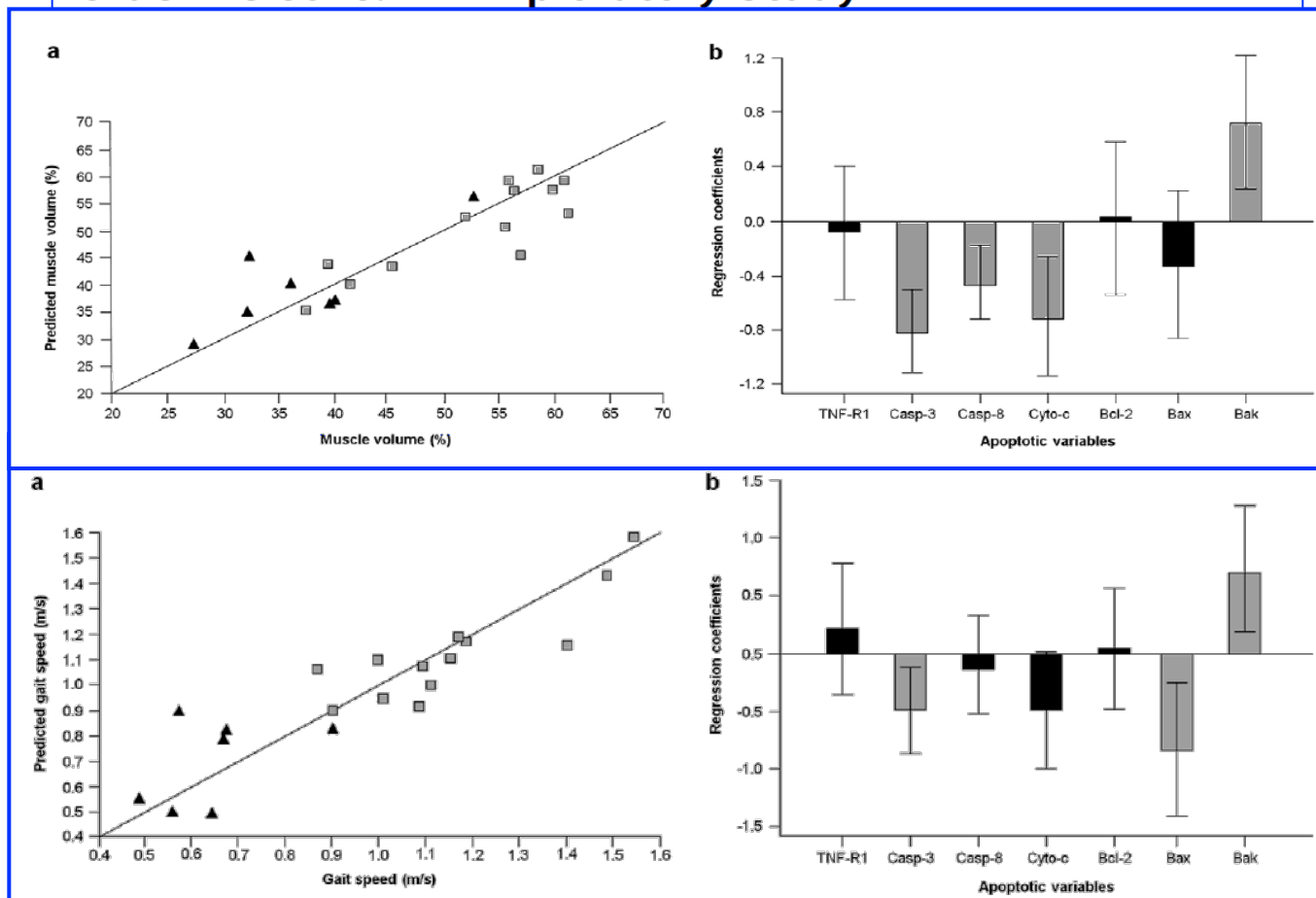


Mitochondrial apoptotic signaling is elevated in rat gastrocnemius muscle at **advanced age**, likely contributing to the age-related muscle loss. Activation of mitochondrial apoptotic signaling may be due to modification of the Bcl-2 proteins pattern of expression, possibly supported by **enhanced levels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

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

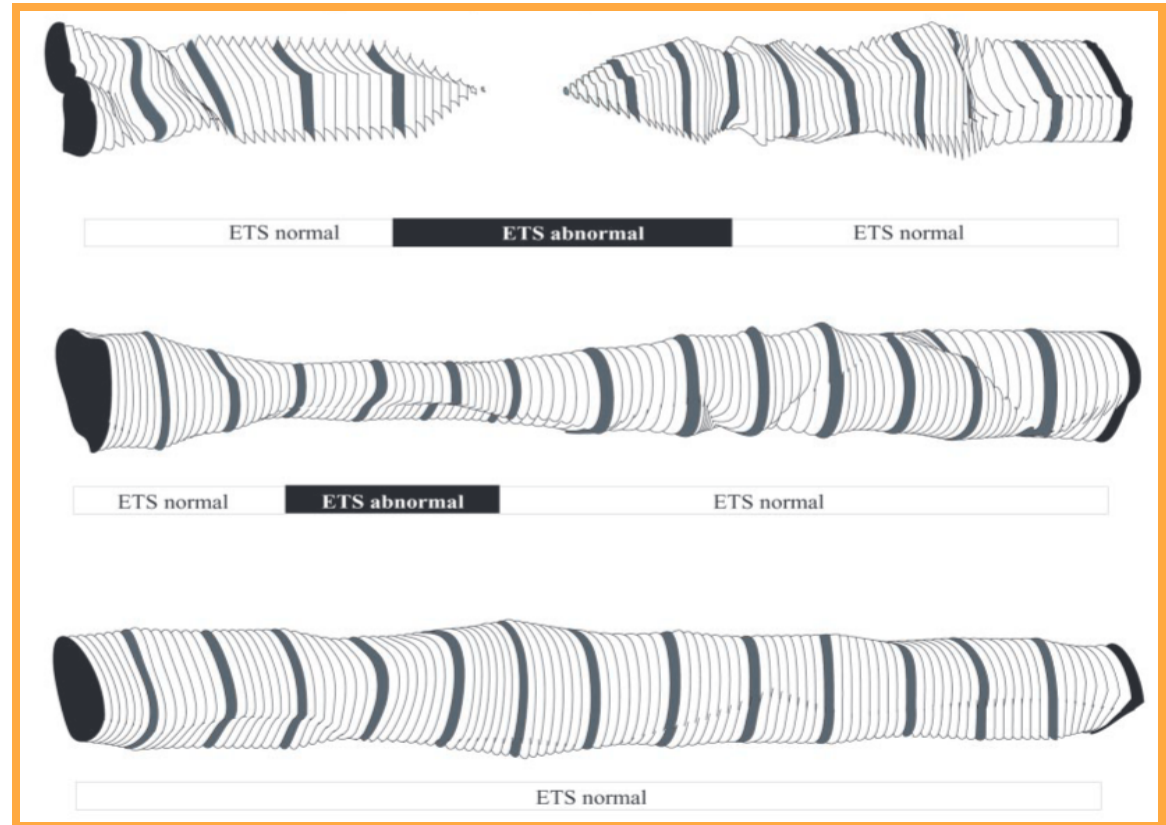
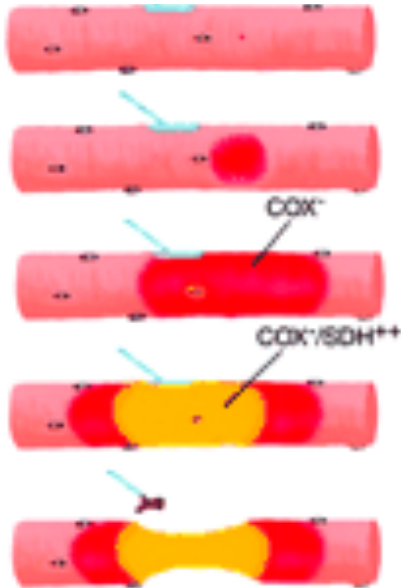
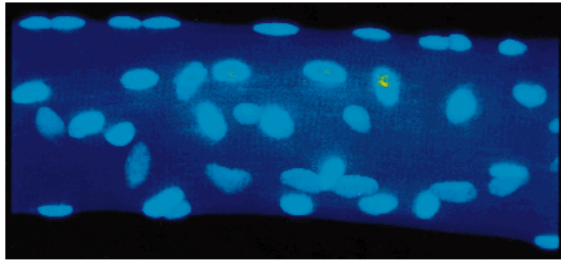


Skeletal Muscle Apoptotic Signaling Predicts Thigh Muscle Volume and Gait Speed in Community-Dwelling Older Persons: An Exploratory Study



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.

NUTRITION IN THE AGE-RELATED DISABLEMENT PROCESS

M. INZITARI^{1,2}, E. DOETS³, B. BARTALI⁴, V. BENETOU⁵, M. DI BARI⁶, M. VISSER⁷, S. VOLPATO⁸,
G. GAMBASSI⁹, E. TOPINKOVA¹⁰, L. DE GROOT³, A. SALVA¹ FOR THE INTERNATIONAL
ASSOCIATION OF GERONTOLOGY AND GERIATRICS (IAGG) TASK FORCE FOR NUTRITION
IN THE ELDERLY¹¹

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)	



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Journal of Nutritional Biochemistry 21 (2010) 1–13

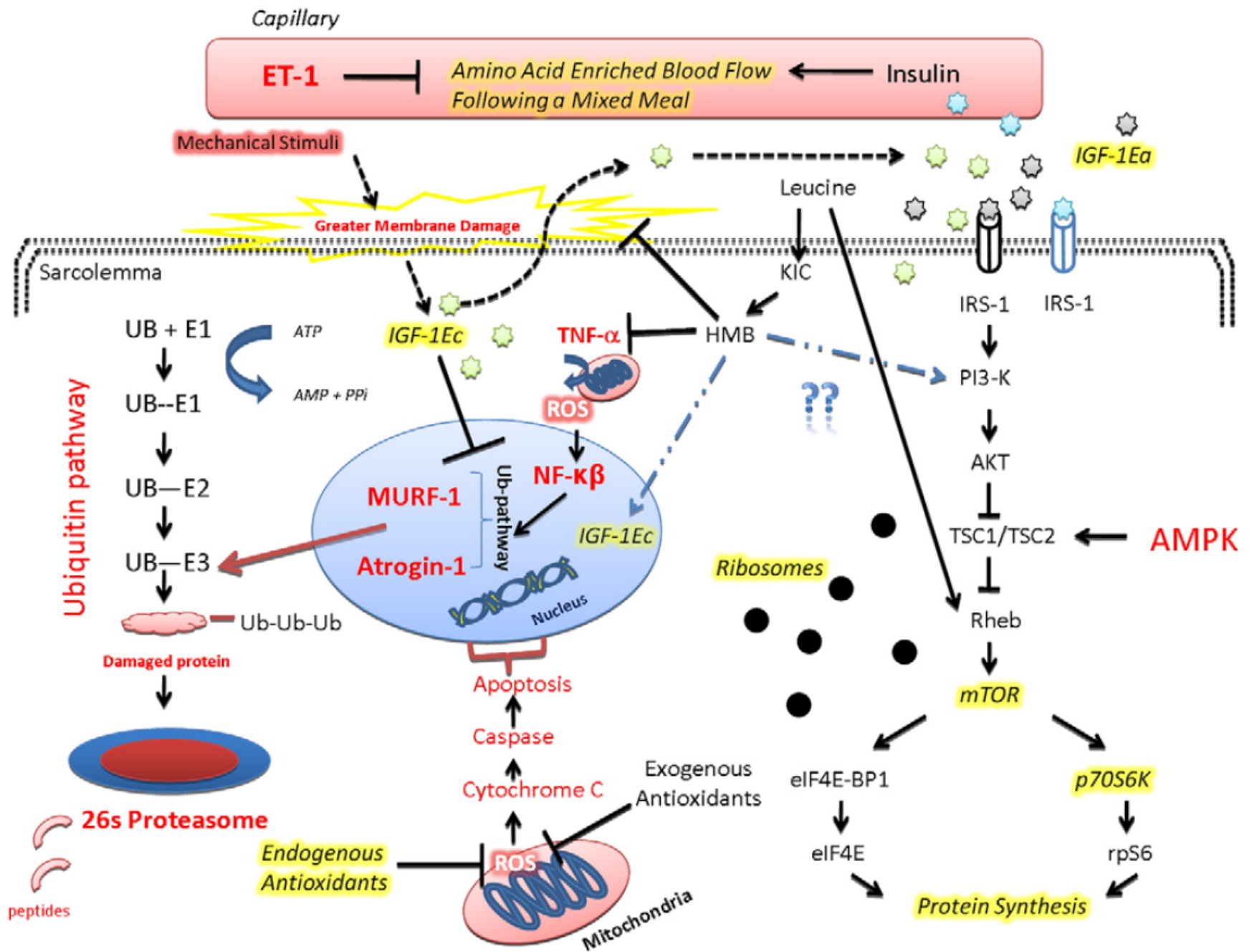
**Journal of
Nutritional
Biochemistry**

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



Review Article

Rationale for Antioxidant Supplementation in Sarcopenia

Francesco Cerullo,¹ Giovanni Gambassi,¹ and Matteo Cesari²

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 Mosoni³

³INRA, 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 ⁴INRA, 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.

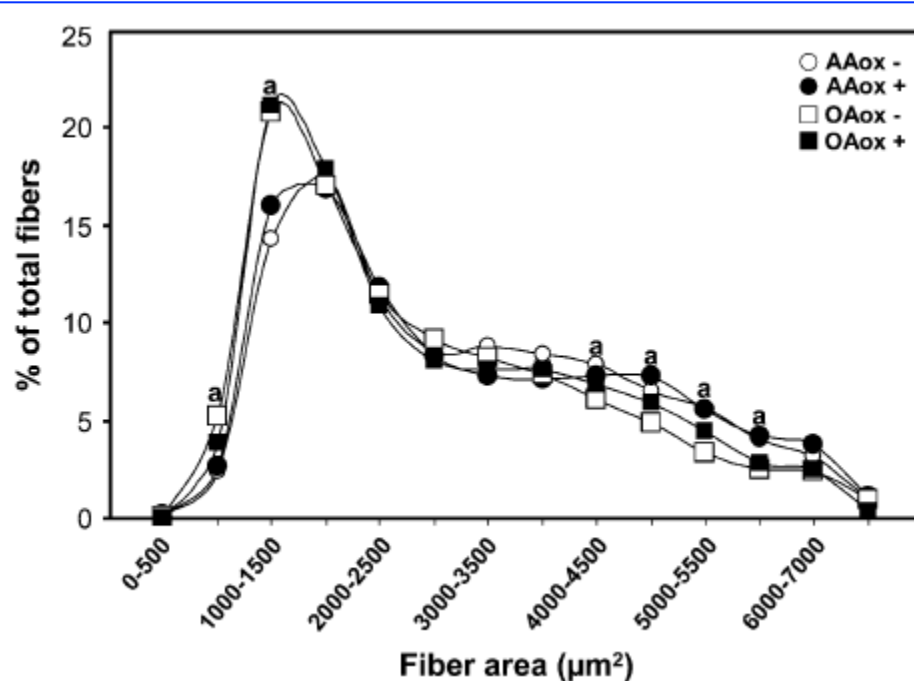


TABLE 2 Body, skeletal muscle, and organ weights in adult and old rats supplemented (Aox+) or not (Aox-) with antioxidants¹

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

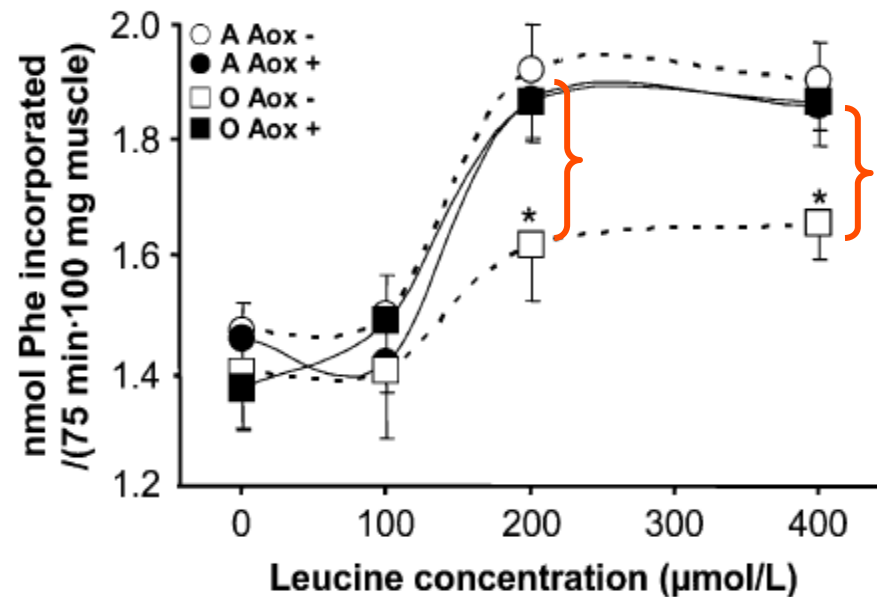


FIGURE 2 Dose-response curves for leucine stimulated muscle protein synthesis in adult (A) and old (O) rats supplemented (Aox+) or not (Aox-) with antioxidants for 7 wk. Rate of protein synthesis was measured as in vitro incorporation of ^{14}C phenylalanine into epitrochlearis muscles in the presence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

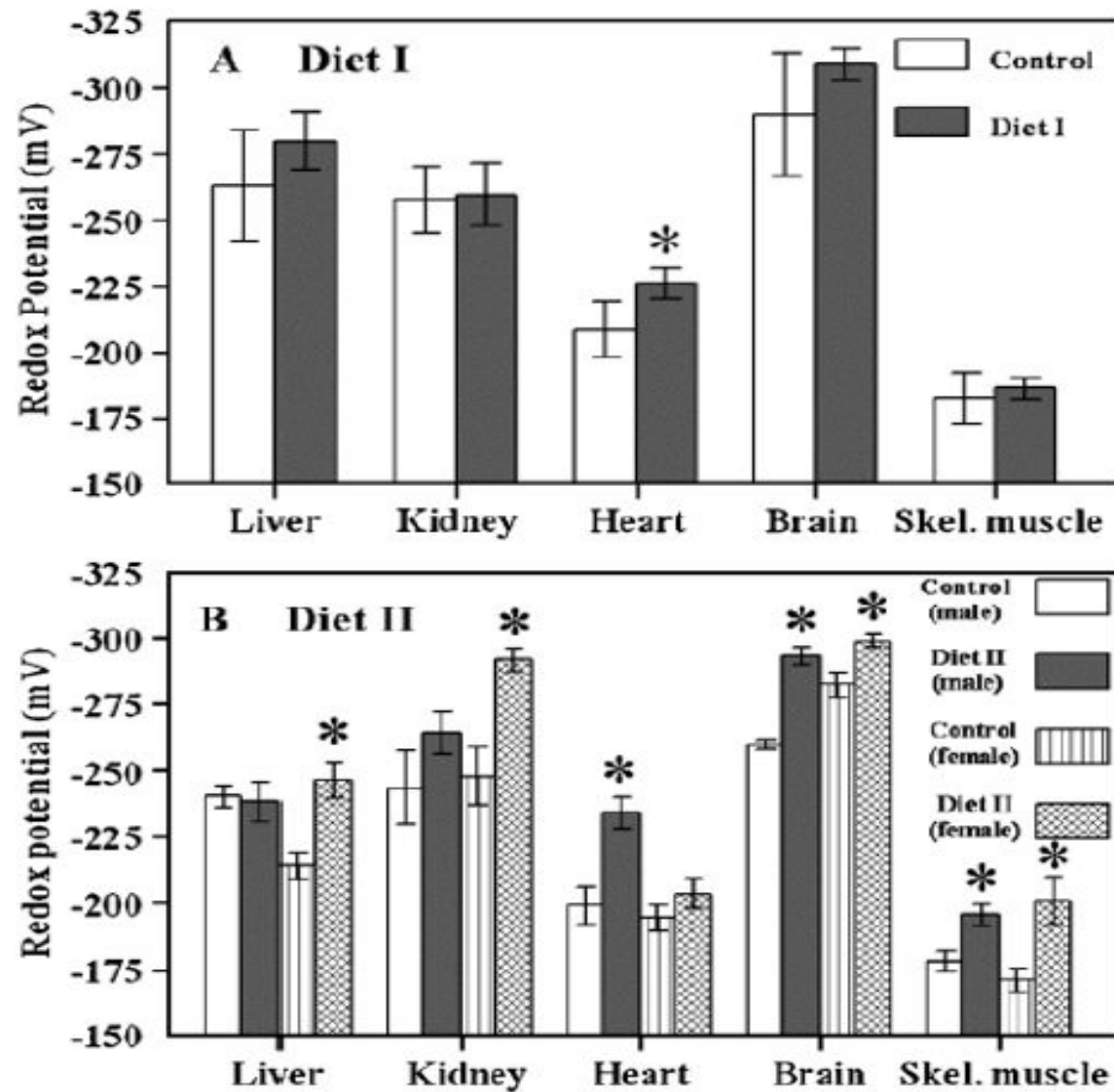
Effect of antioxidant-enriched diets on glutathione redox status in tissue homogenates and mitochondria of the senescence-accelerated mouse

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.

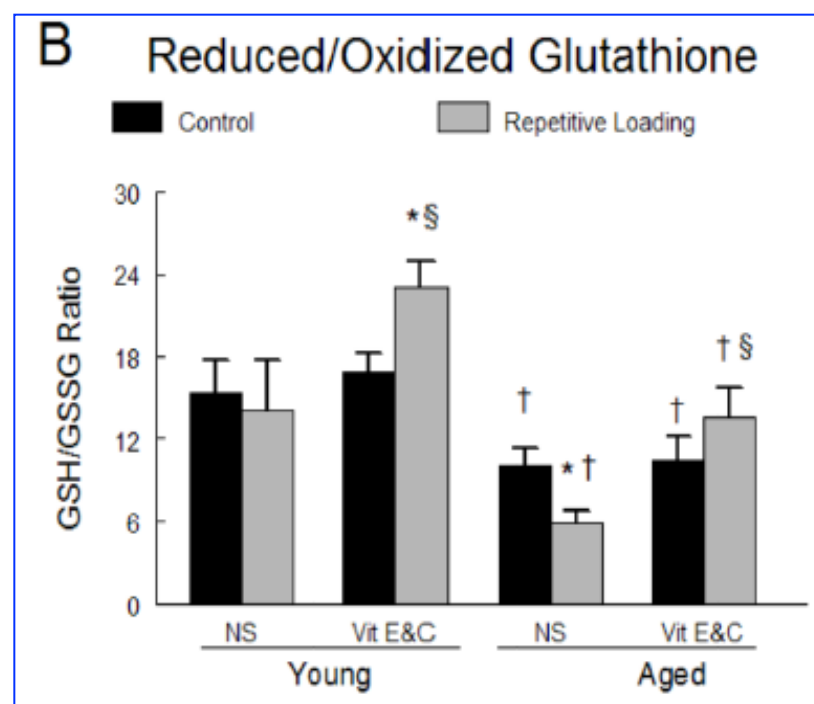
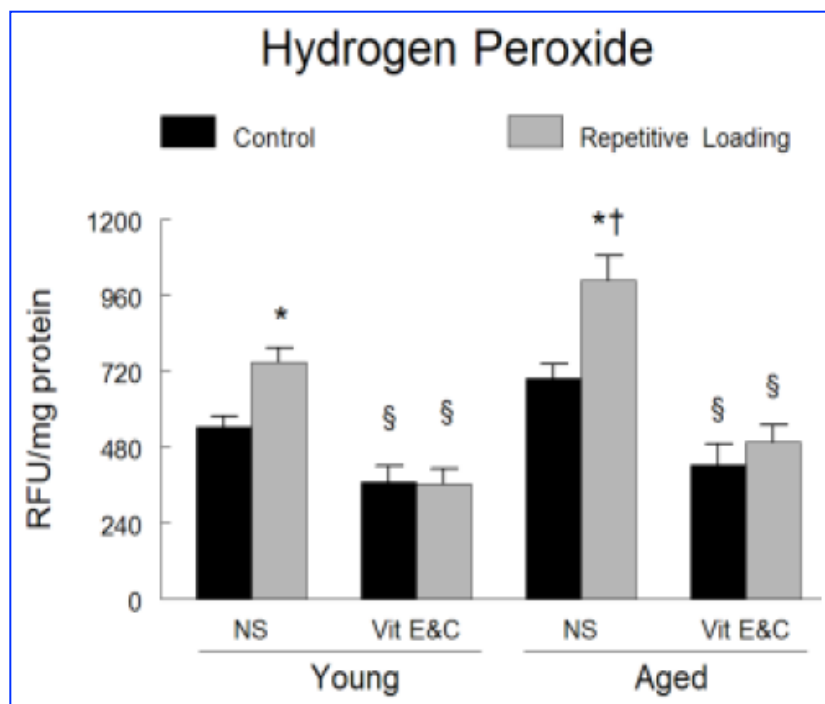
Effect of antioxidant-enriched diets on glutathione redox status in tissue homogenates and mitochondria of the senescence-accelerated mouse

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

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



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



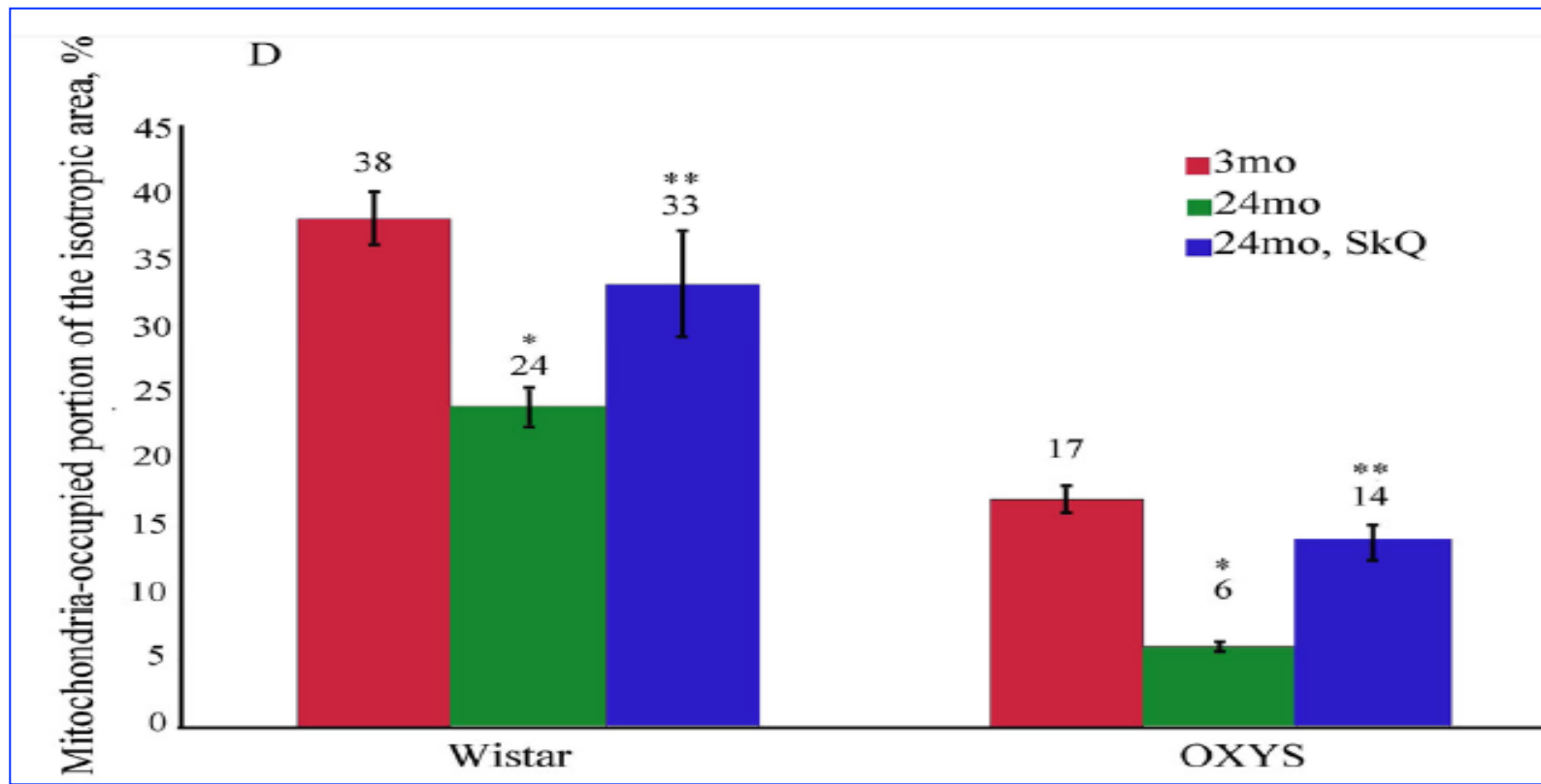
conclusion

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

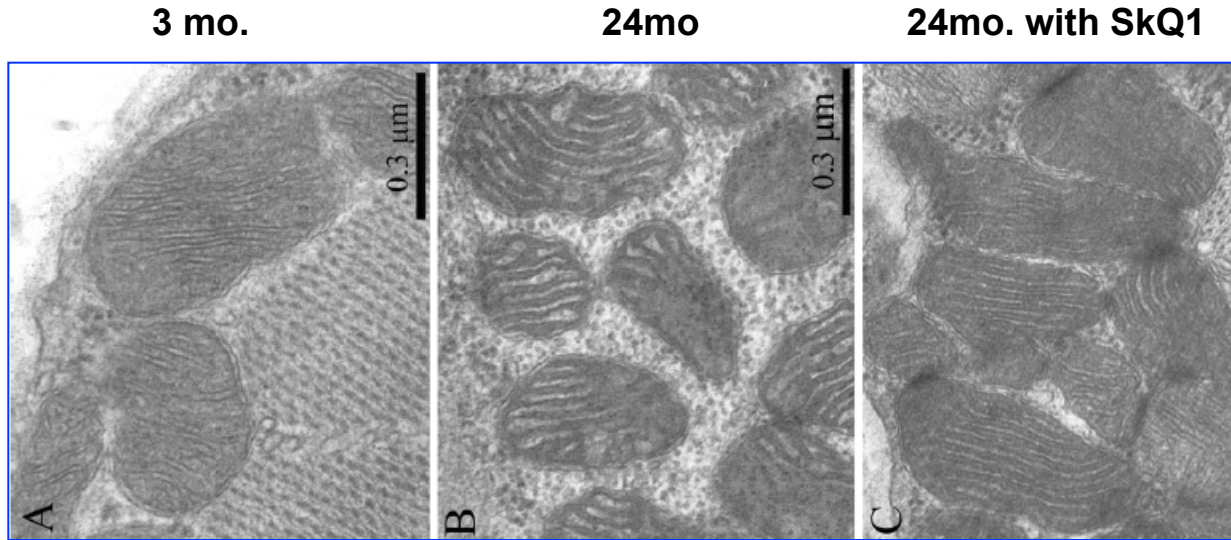
Statistic analysis of the volume occupied by the skeletal muscle mitochondria



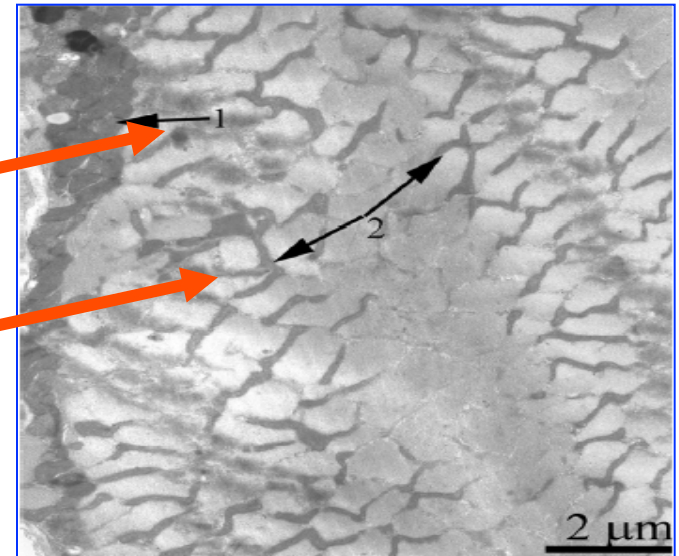
mitochondria-targeted antioxidant SkQ1[10-(6'-plastoquinonyl) decyltriphenylphosphonium]

Antioxidant SkQ1 delays sarcopenia-associated damage of mitochondrial ultrastructure

AGING, February 2014, Vol. 6 No.2



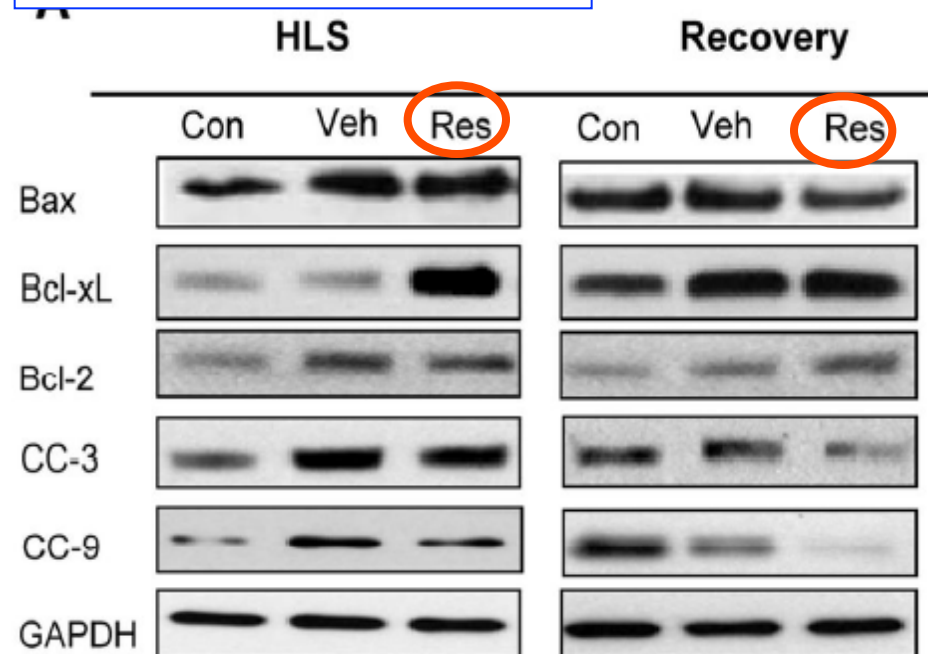
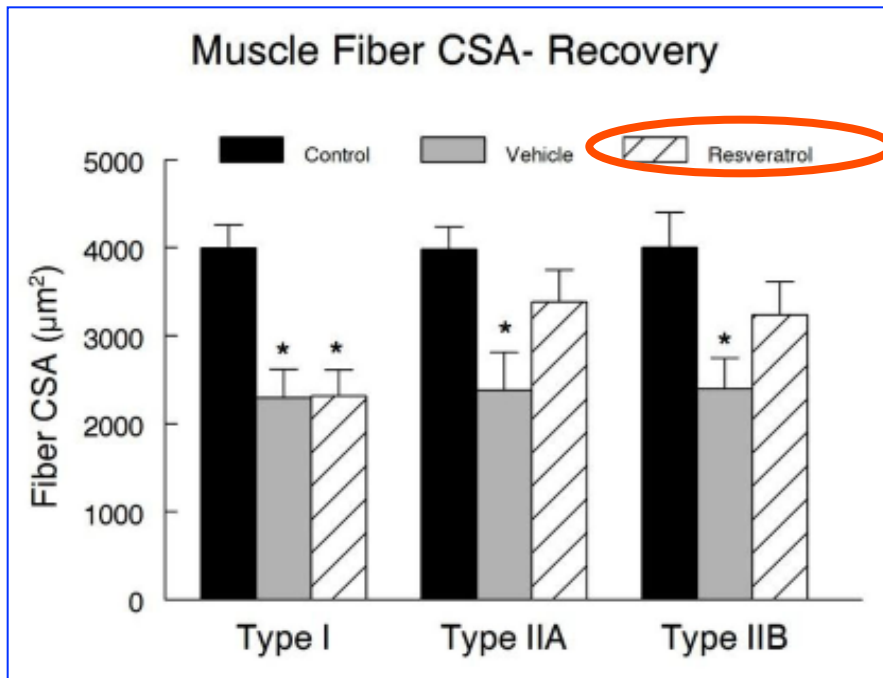
A fragment of the muscle fiber from a 24-month-old Wistar rat treated with SkQ1. Subsarcolemmal population of mitochondria (1) interfibrillar stretched mitochondria (2).



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

PlosOne, 2013

APOPTOTIC SIGNALLING

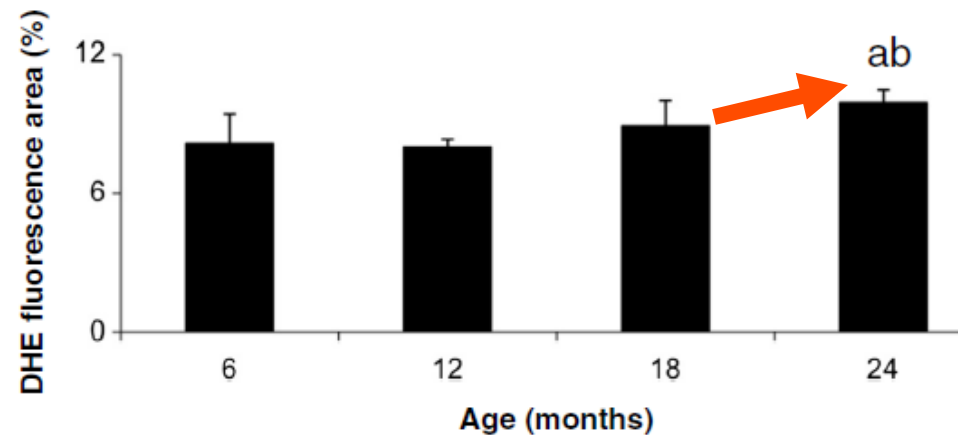


The data show that resveratrol supplementation **improved muscle mass** during reloading after hindlimb suspension. Although resveratrol **did not prevent fiber atrophy** during the period of disuse, it **increased the fiber cross sectional area of type IIA and IIB fibers** in response to reloading.

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



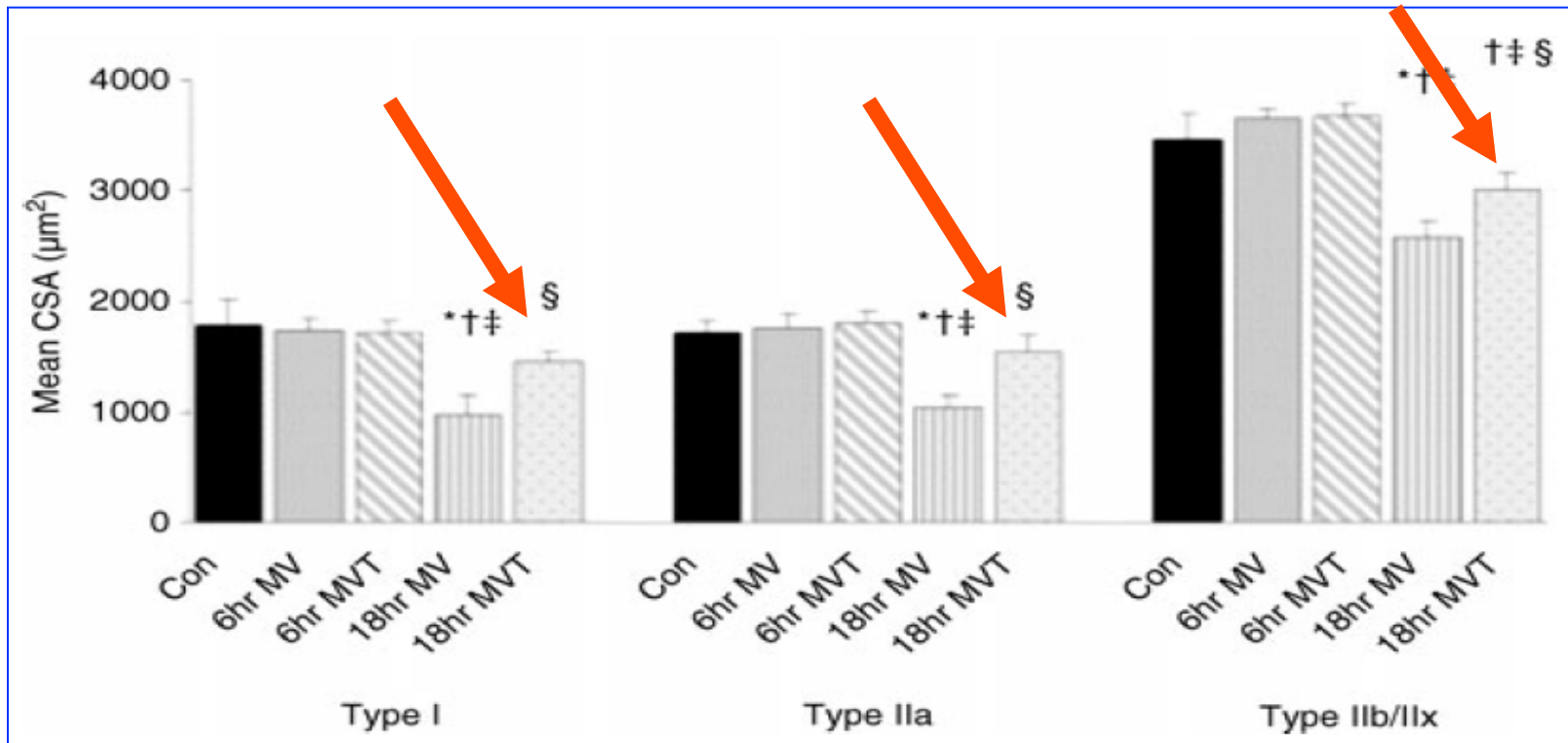
Enzyme activity and hydrogen peroxide levels in aging skeletal muscle

	Age (months)				Gene expres
	6 (n = 16)	12 (n = 18)	18 (n = 12)	24 (n = 12)	
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}	

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)



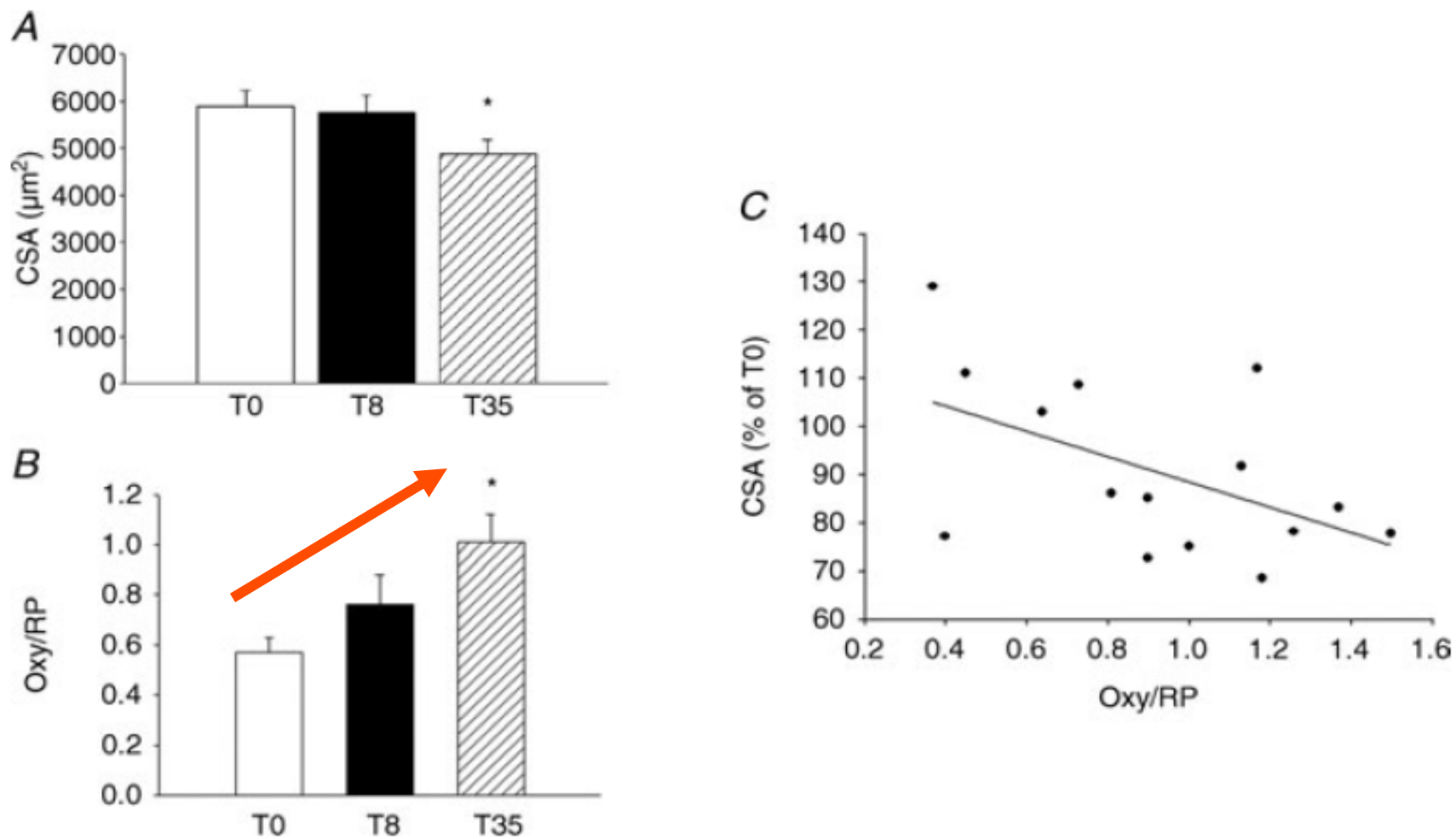
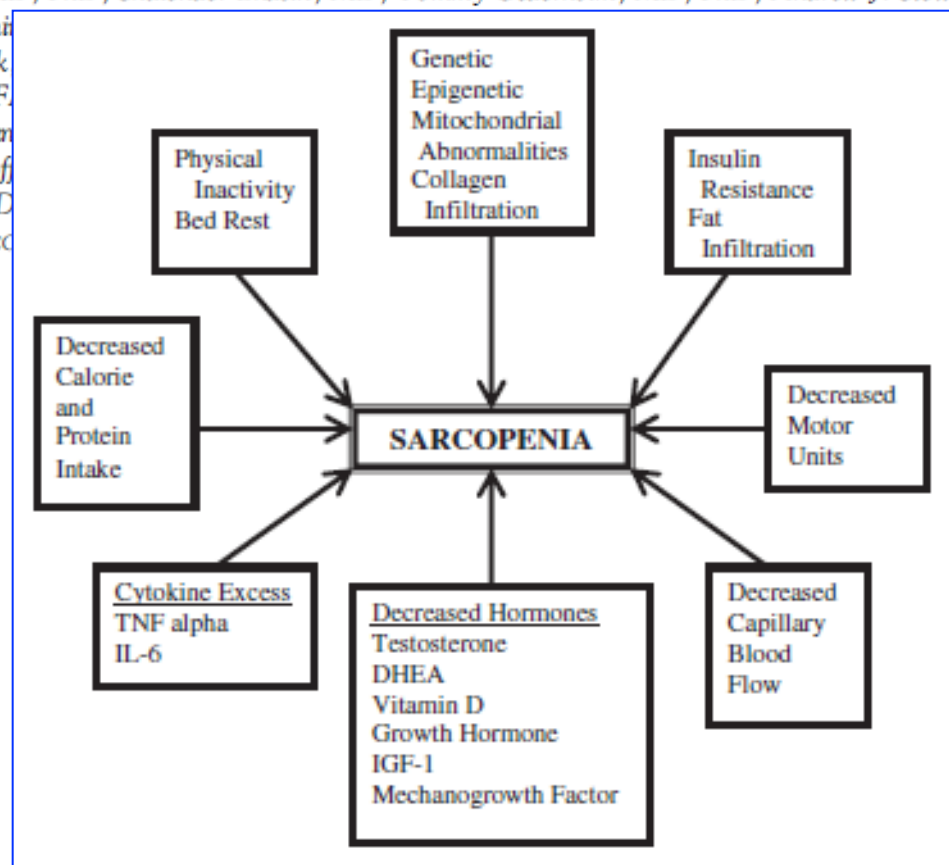


Figure 4. The impact of 8 (T8) and 35 (T35) days of bed rest on cross-sectional area (CSA) of muscle fibres and on protein oxidation (Oxy/RP) of muscle samples from the vastus lateralis muscle of humans
A, mean values of CSA of muscle fibres before bed rest (T0) and at T8 and T35. **B**, protein oxidation 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

muscle	VL	gas	sol	sol	dia
species	humans	rat & mice	rat & mice	rat & mice	rat & mice humans
model	BR, imm., ULLS	HU	HU	imm.	MV
rate of atrophy	5-25% in 23 w	11% in 14d	24% in 14d	50% in 8d	In 15-18% 18h
					
slow phenotype					
rate of oxidative metabolism					
relative decrease in load & in neuromuscular activity					
extent of ROS production					
rate of increased proteolysis due to large scale oxidative effect					
	Less determinant			More determinant	

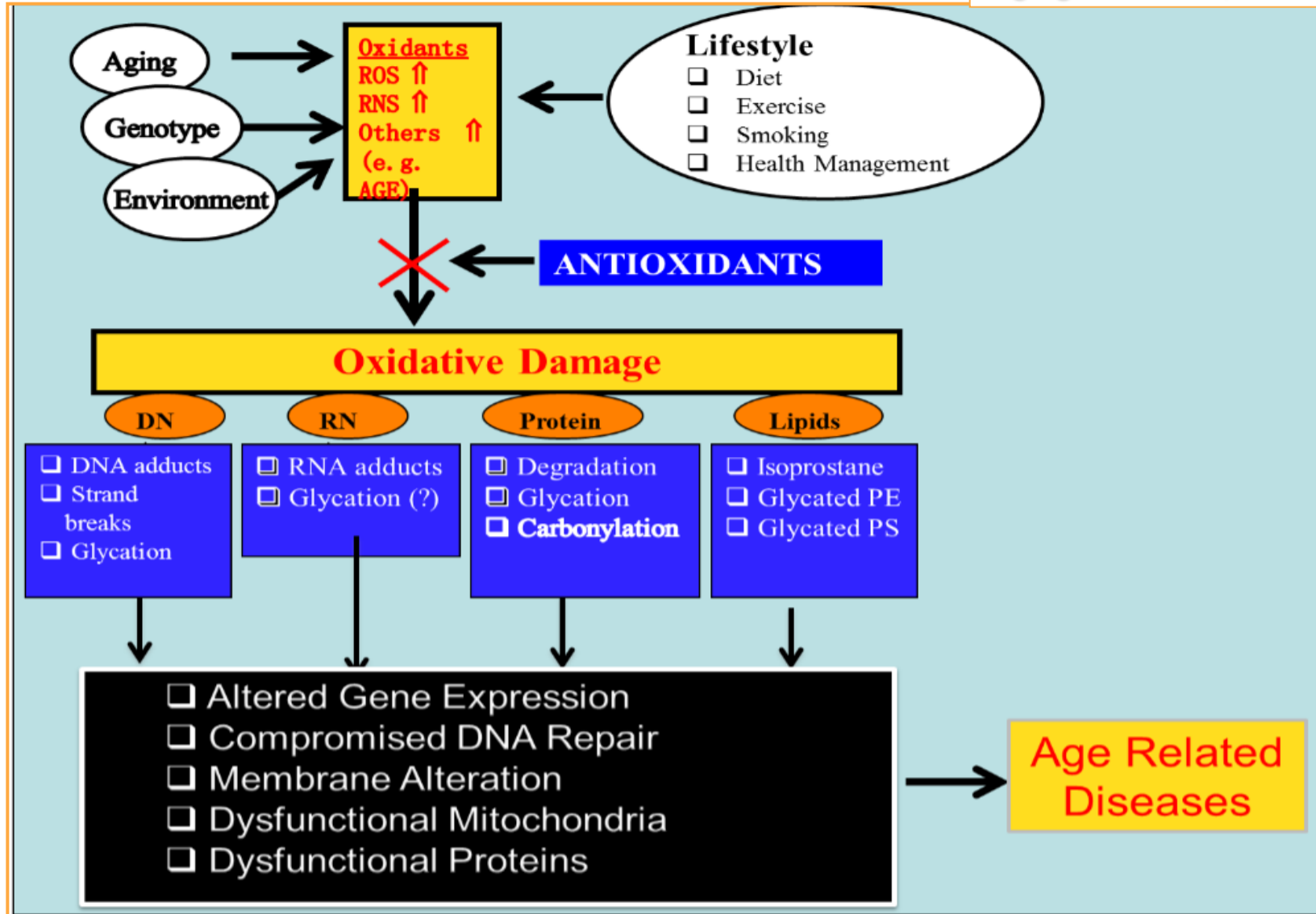
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 wart Coats, DM, DSc,
 D, Roger A. Fielding, PhD,
 r-Zadeh, MD, PhD, MPH,
 rizio Muscaritoli, MD,
 PhD, FESC,
 as W. Storer, PhD,
 D. Anker, MD, PhD, THE



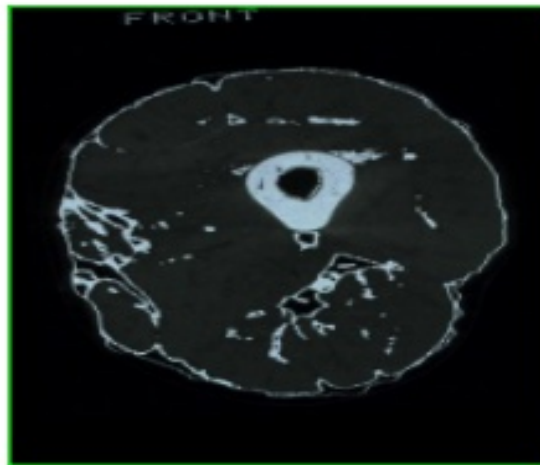
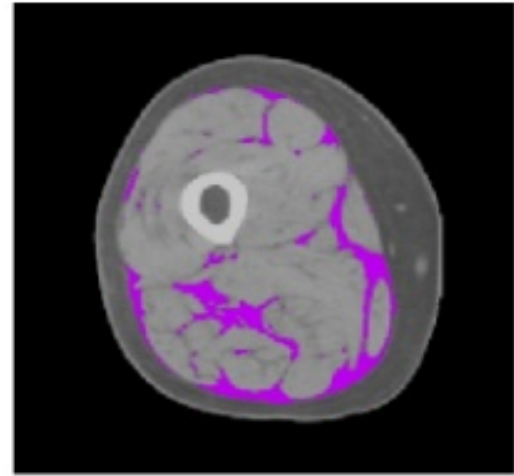
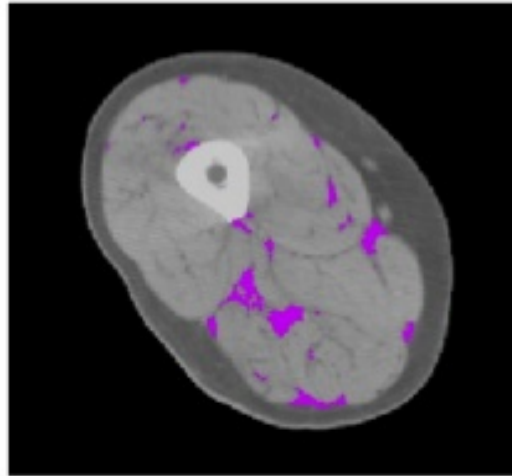
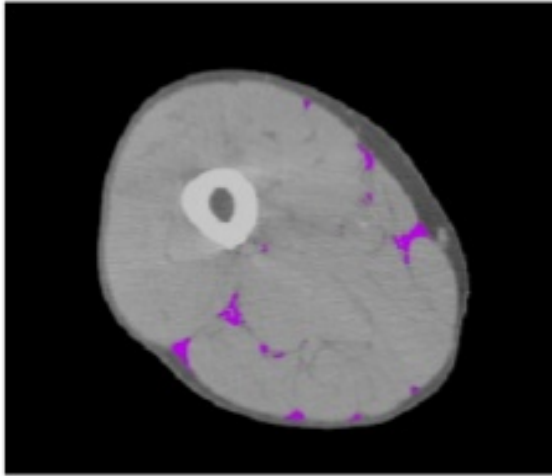
Lifestyle and Advanced Glycation End Products (AGEs) Burden: Its Relevance to Healthy Aging

Chandan Prasad^{1*}, Victorine Imrhan¹, Francesco Marotta², Shanil Juma¹ and Parakat Vijayagopal¹

Aging & Disease, June 2014

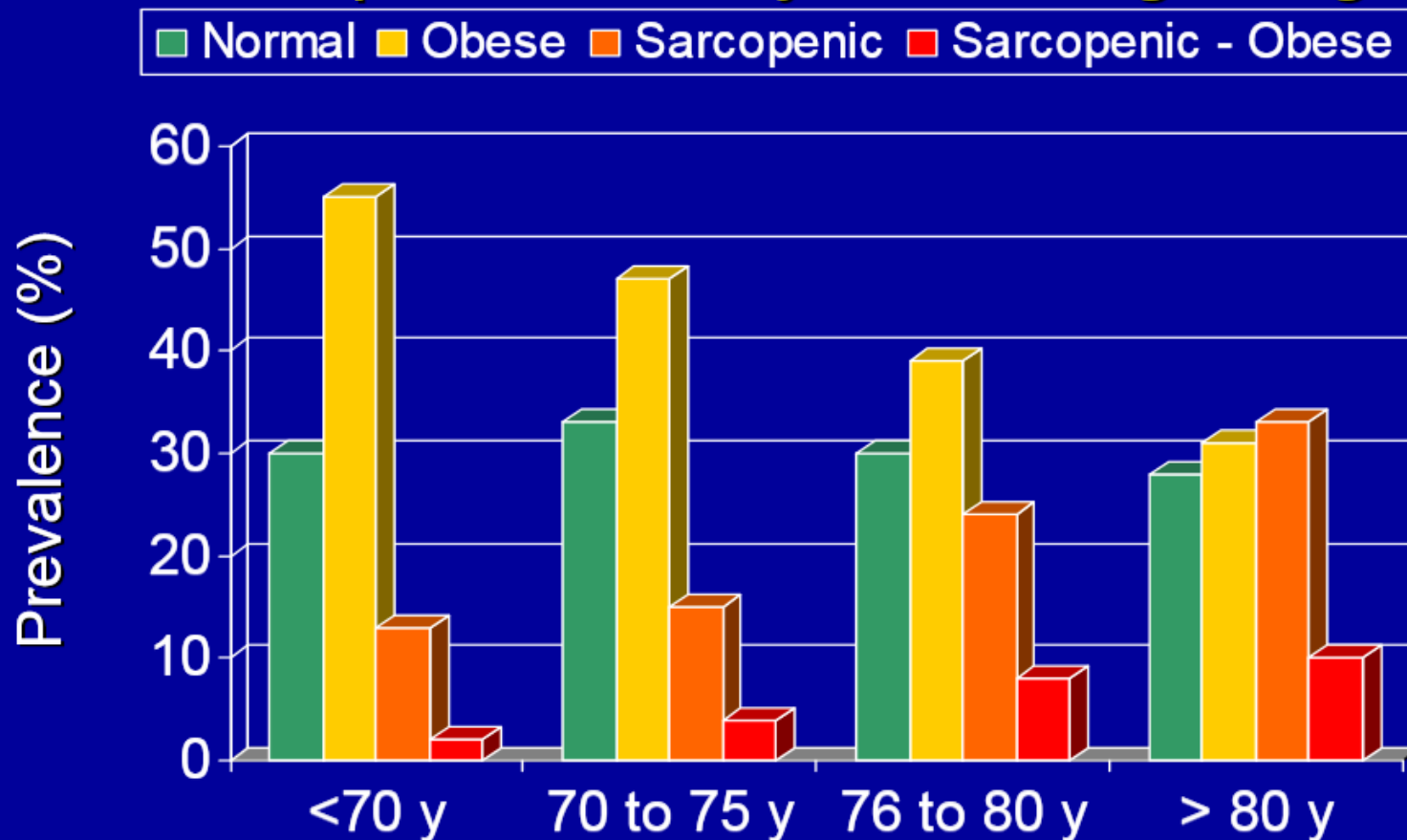


With Sarcopenic Obesity increases in Intermuscular Fat



and
Intramuscular fat:
Low Density
Lean Tissue by CT

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



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