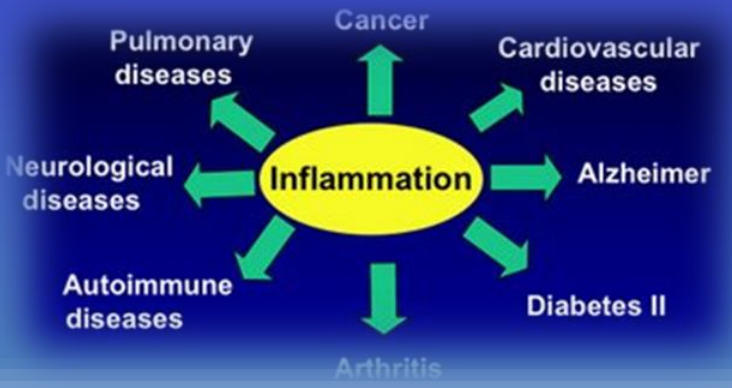
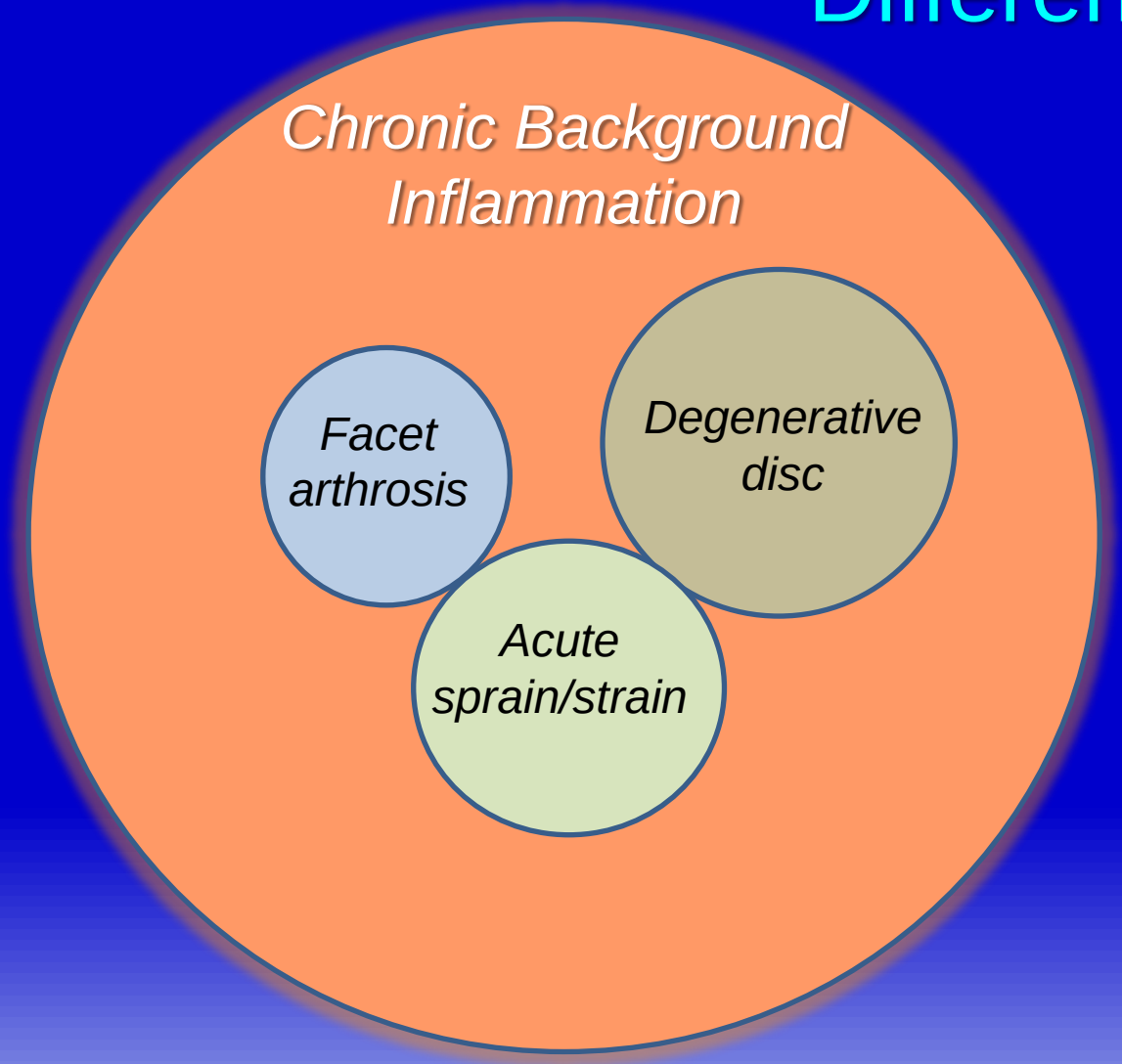
Metabolic Inflammatory Factors That Mimic or Contribute to NMS Disorders

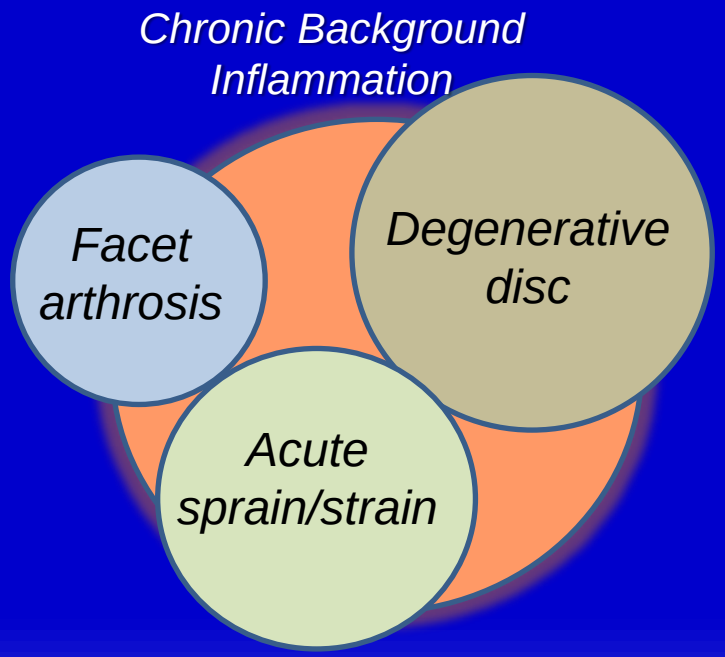
The Greatest Complicating Factor in Chiropractic Treatment Success - Inflammation



Same Condition, Different Outcomes

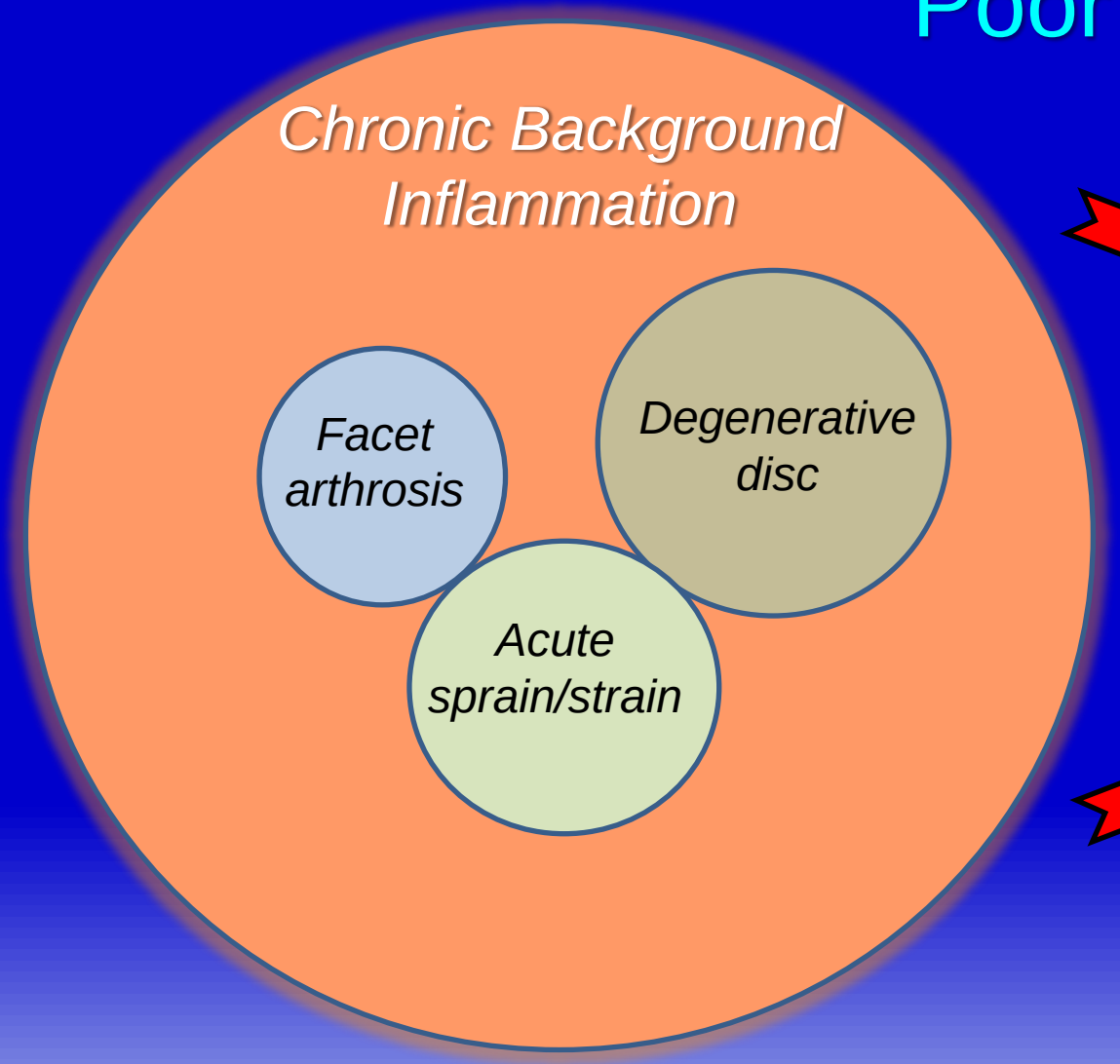


Incomplete outcome



Good outcome

What Drives Poor Outcomes



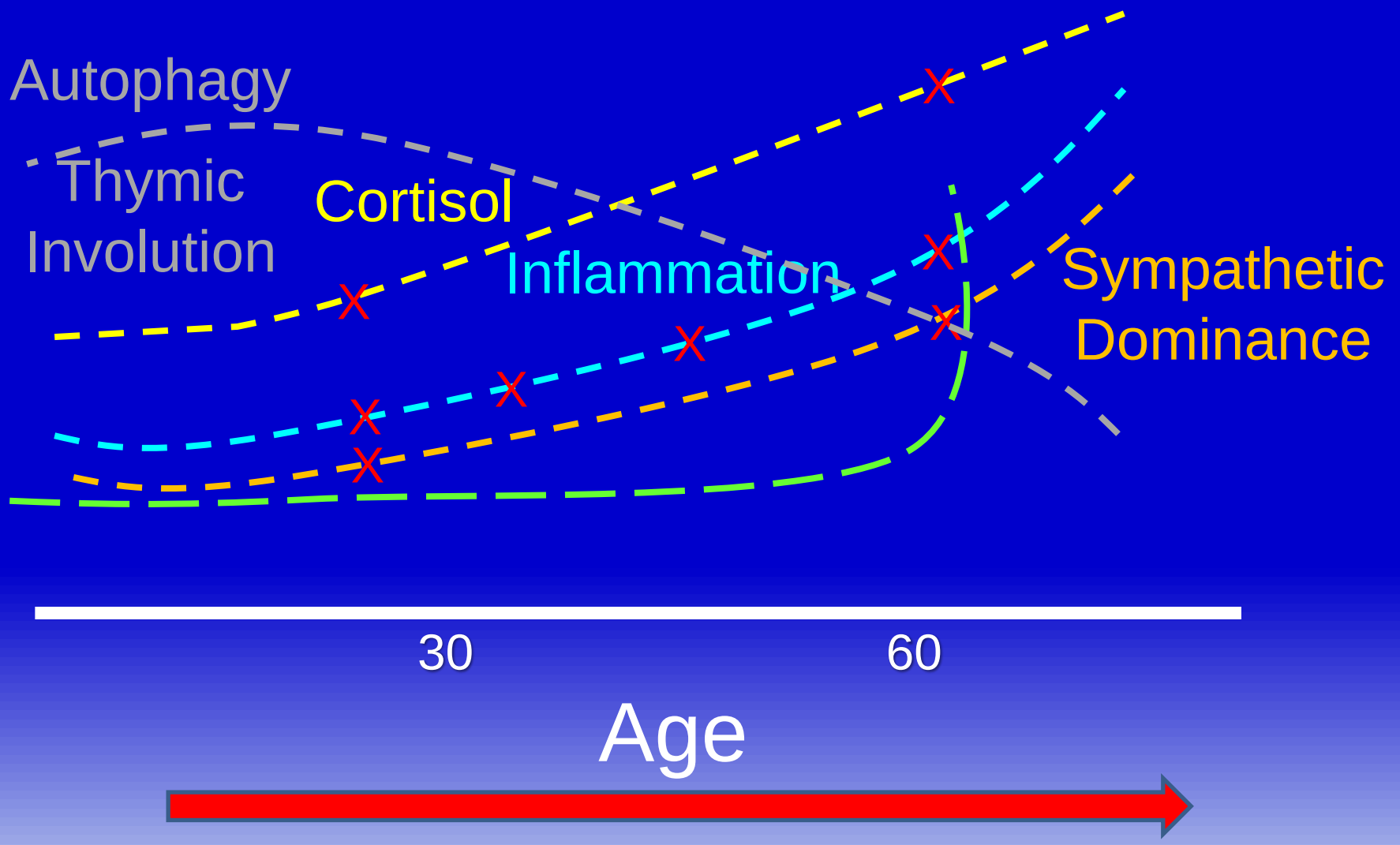
Incomplete outcome

DAMPs – Damage associated molecular patterns; tissue degeneration

HAMPs – Homeostatic associated molecular patterns; metabolic induced systemic inflammation

PAMPs – Pathogen associated molecular patterns; infection

Biomarkers that Correlate With the Pace of Aging

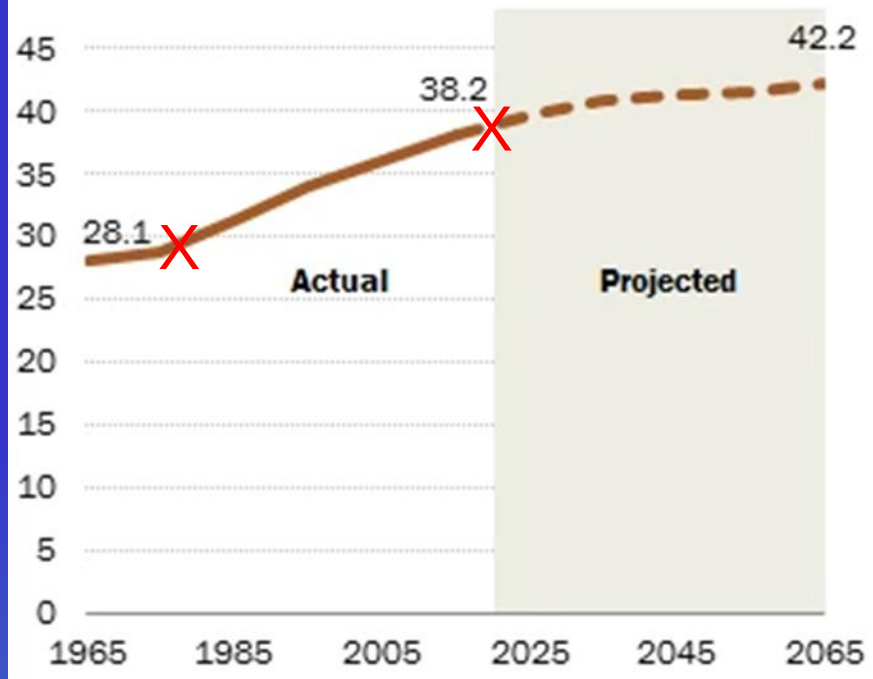


The Growing Problem with Inflammation

	Projected Change 1985-2020
Age 15-44 years	0%
Age 45-64 years	+75%
Age >65 years	+60%
Population Growth	+28%

FIGURE 2.10

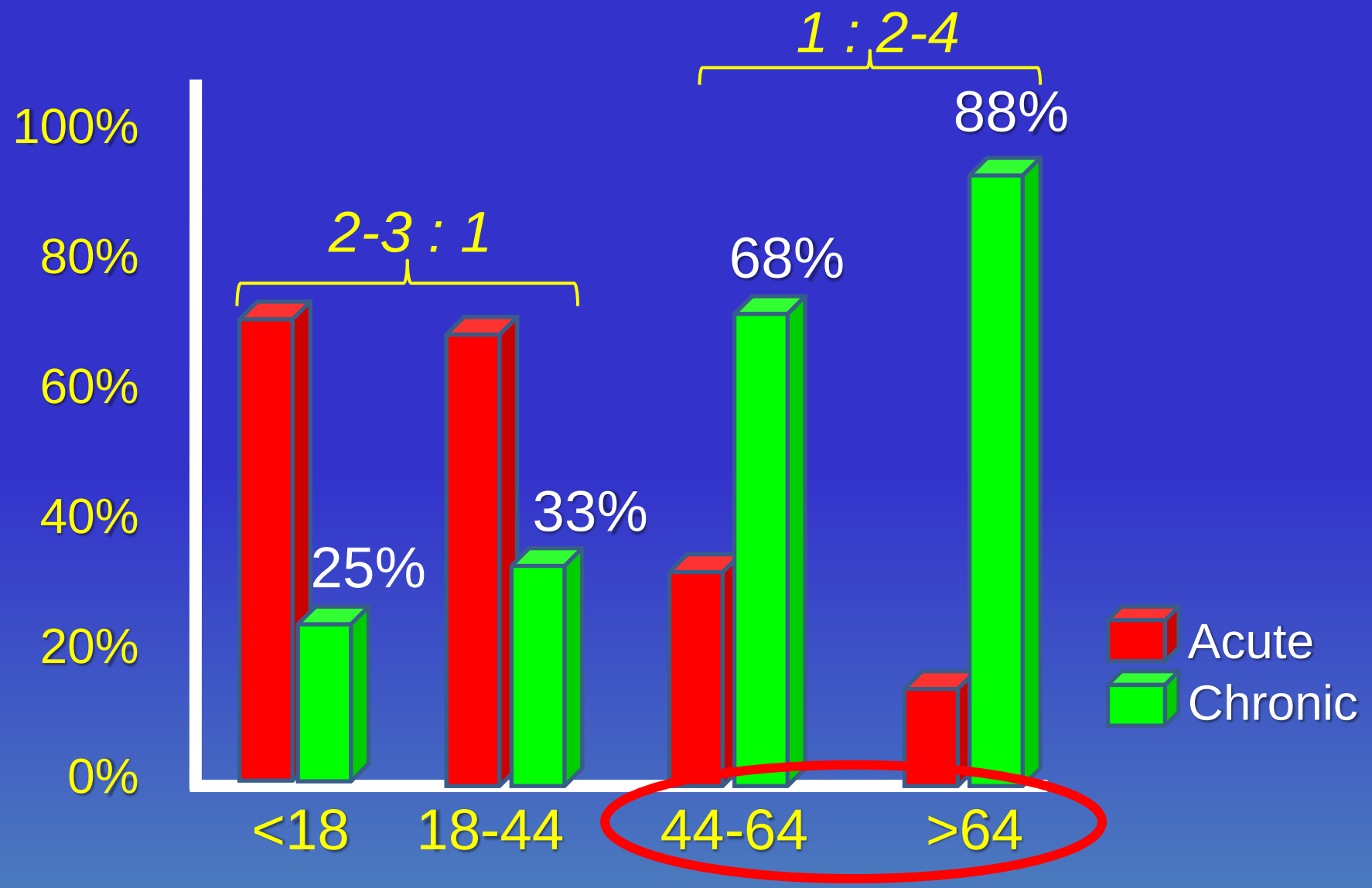
U.S. Median Age Projected to Rise to 42 by 2065



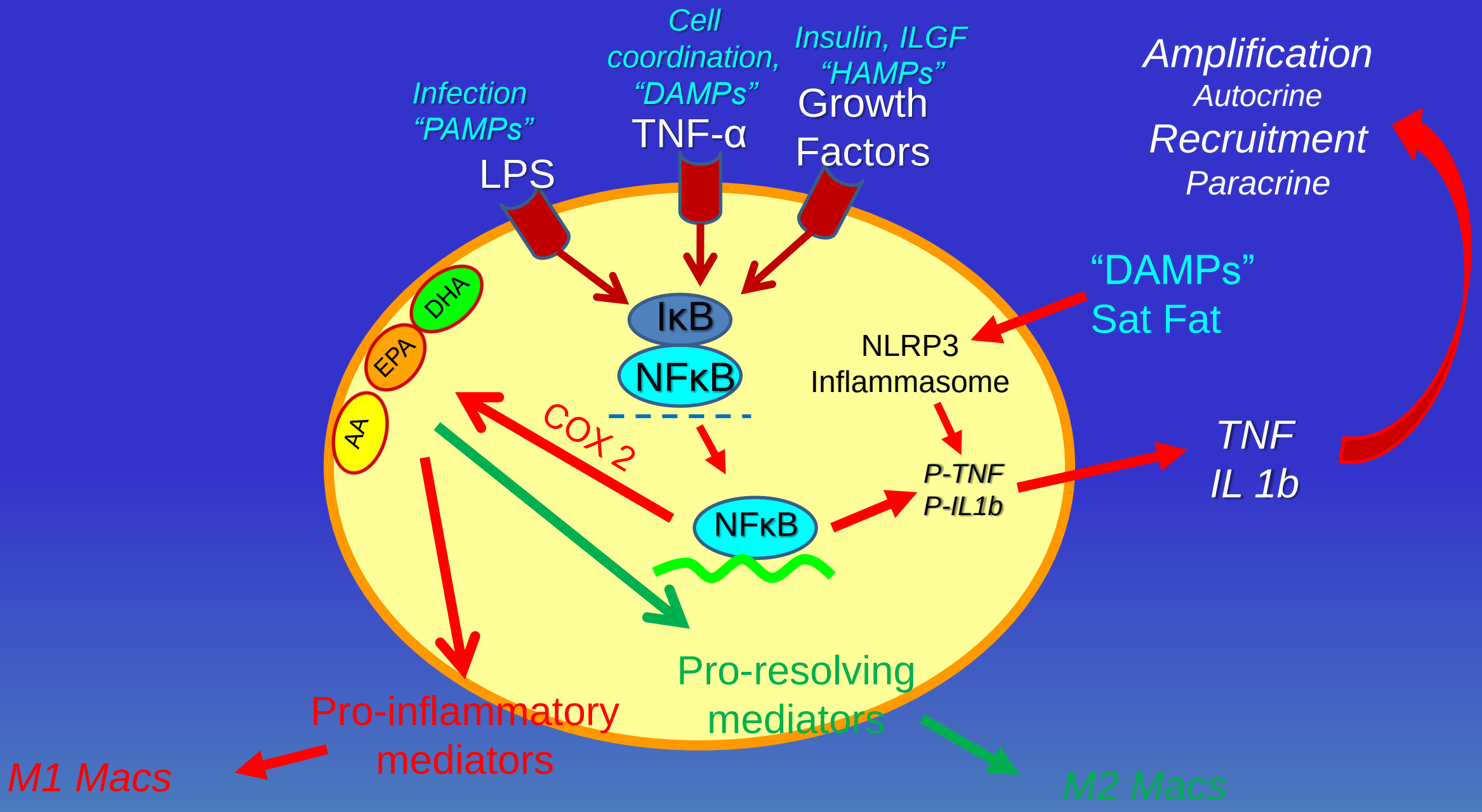
Source: Pew Research Center estimates for 1965-2015 based on adjusted census data; Pew Research Center projections for 2015-2065

PEW RESEARCH CENTER

Changing Face of Disease



Health Disorders by Age Bracket


Infection
"PAMPs"
LPS
Cell
coordination,
"DAMPs"
TNF-α
Insulin, ILGF
"HAMPs"
Growth
Factors
Amplification
Autocrine
Recruitment
Paracrine
"DAMPs"
Sat Fat
DHA
EPA
AA
IκB
NFκB
NLRP3
Inflammasome
COX 2
P-TNF
P-IL1b
NFκB
TNF
IL 1b
Pro-inflammatory
mediators
Pro-resolving
mediators
M1 Macs
M2 Macs

When Inflammation Prevents Rehabilitation

"A greater proportion of M1 macrophages are present in muscle at both 3 and 6 months after IVD lesion, and adipose tissue at 6 months. Total number of macrophages is unchanged. At 6 months, expression of TNF is increased in adipose and connective tissue and the proportion of TNF expressed by M1 macrophages is increased."

James et al. MACROPHAGE POLARIZATION CONTRIBUTES TO LOCAL INFLAMMATION AND STRUCTURAL CHANGE IN THE MULTIFIDUS MUSCLE AFTER INTERVERTEBRAL DISC INJURY. European Spine Journal, 2018;27:1744–1756.

Radiculitis

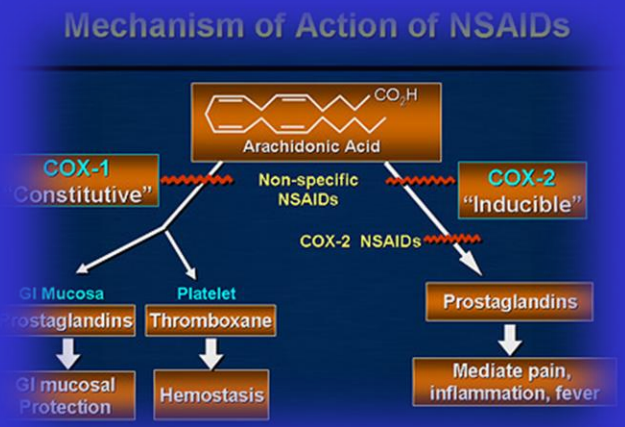
Compression or Inflammation?

"Sciatic symptoms due to lumbar disc herniation are likely to be caused not solely by mechanical compression of the nerve root, but also by pain-inducing elements from inflammatory processes."

"Regarding M1-related cytokines, high levels of TNF-α, TNFR1, IL-6, IL-8, and IFN-γ were all associated high VAS scores. Results regarding M2-related cytokines revealed the opposite: high levels of both IL-4 and IL-10 were associated with lower VAS scores."

Djurik et al. THE CONTRADICTORY EFFECT OF MACROPHAGE-RELATED CYTOKINE EXPRESSION IN LUMBAR DISC HERNIATIONS: A SYSTEMATIC REVIEW. European Spine Journal (2020) 29:1649–1659.

NSAIDs for Inflammation

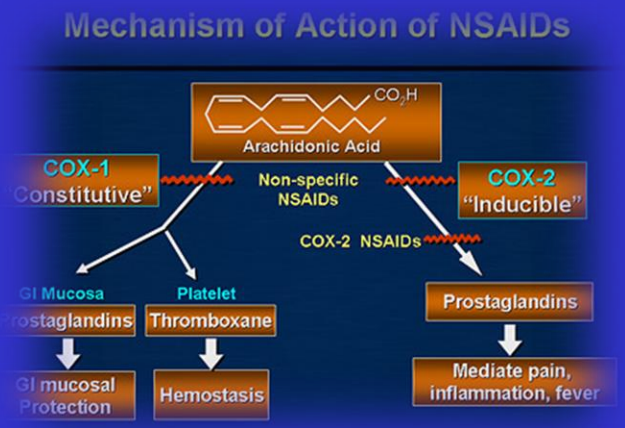


Chronic NSAID use is associated with significant adverse event rates.

While NSAIDs may offer short term symptom relief, they are ***"resolution toxic".***

Acute stage NSAID use increases the risk of transitioning to chronic pain.

NSAIDs for Inflammation

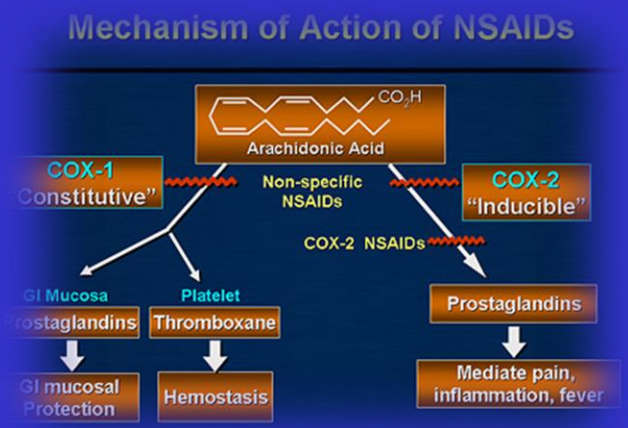


Inexpensive solution? - Treatment costs NSAID complication are $1.9 billion annually.

While NSAIDs may offer short term symptom relief they are documented to increase radiographic progression of degeneration – "Resolution toxic".

Several herbal phenolics actually provide comparable symptomatic relief and are trophic rather than dystrophic.

NSAIDs and Inflammation



100,000 hospitalizations, 20,000 deaths annually from GI bleeding events.

1.7 million hospitalizations in the past 20 years.

Why? - Between 20-30% of US adults take them daily.

NSAIDs Are Resolution Toxic

"It is now very apparent that certain widely used drugs, as well as those in experimental settings, are "resolution-toxic" in that they derange or impair timely and/or complete resolution."

"This is most notable in the case of the inhibition of COX-2 with selective COX-2 inhibitors, where these inhibitors block the production of PGE2 and PGD2, which play important roles in bringing about resolution. Their findings also underscore the role of COX-2 and its products in both the initiation of acute inflammatory response as well as its resolution."

Sherhan et al. RESOLUTION OF INFLAMMATION: STATE OF THE ART, DEFINITIONS AND TERMS. FASEB J. 2007 Feb; 21(2): 325–332.

Resolution Toxicity of COX Inhibition

"In conclusion, in our in vitro system of endothelial inflammation, DHA reduced inflammation and induced a pro-resolution profile of oxylipins, while hydrocortisone blunted both pro-inflammation and pro-resolution pathways."

Motta et al. OXYLIPIN PROFILING IN ENDOTHELIAL CELLS IN VITRO – EFFECTS OF DHA AND HYDROCORTISONE UPON AN INFLAMMATORY CHALLENGE. Prostaglandins and Other Lipid Mediators, 2019;144:106352.

PAIN

Acute inflammatory response via neutrophil activation protects against the development of chronic pain

Marc Parisien[1]†, Lucas V. Lima[2]†, Concetta Dagostino[3]†, Nehme El-Hachem[1], Gillian L. Drury[1], Audrey V. Grant[1], Jonathan Huising[4], Vivek Verma[1], Carolina B. Meloto[1], Jaqueline R. Silva[5], Gabrielle G. S. Dutra[2], Teodora Markova[2], Hong Dang[6], Philippe A. Tessier[7], Gary D. Slade[8], Andrea G. Nackley[9], Nader Ghasemlou[5], Jeffrey S. Mogil[2]*, Massimo Allegri[10,11]*, Luda Diatchenko[1]*

The transition from acute to chronic pain is critically important but not well understood. Here, we investigated the pathophysiological mechanisms underlying the transition from acute to chronic low back pain (LBP) and performed transcriptome-wide analysis in peripheral immune cells of 98 participants with acute LBP, followed for 3 months. Transcriptomic changes were compared between patients whose LBP was resolved at 3 months with those whose LBP persisted. We found thousands of dynamic transcriptional changes over 3 months in LBP participants with resolved pain but none in those with persistent pain. Transient neutrophil-driven up-regulation of inflammatory responses was protective against the transition to chronic pain. In mouse pain assays, early treatment with a steroid or nonsteroidal anti-inflammatory drug (NSAID) also led to prolonged pain despite being analgesic in the short term; such a prolongation was not observed with other analgesics. Depletion of neutrophils delayed resolution of pain in mice, whereas peripheral injection of neutrophils themselves, or S100A8/A9 proteins normally released by neutrophils, prevented the development of long-lasting pain induced by an anti-inflammatory drug. Analysis of pain trajectories of human subjects reporting acute back pain in the UK Biobank identified elevated risk of pain persistence for subjects taking NSAIDs. Thus, despite analgesic efficacy at early time points, the management of acute inflammation may be counterproductive for long-term outcomes of LBP sufferers.

INTRODUCTION

Chronic pain inflicts huge societal costs, in terms of management, loss of work productivity, and effects on quality of life (*1*). Chronic low back pain (LBP) is the most frequently reported chronic pain condition (*2*). LBP is a major problem worldwide: point, 1-month, and 1-year prevalence is 18, 31, and 38%, respectively (*3*). LBP ranks the highest of all chronic conditions in terms of years lived with disability, with its prevalence and burden increasing with age (*4*). Current treatments for LBP often target the immune system and include nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and corticosteroids, although all of these drug classes are minimally effective at best (*5*). Despite advances in the understanding of social, psychological, and genetic factors, as well as brain processes associated with chronic LBP (*6*), we understand very little of the molecular mechanisms underlying the acute-to-chronic pain transition that might lead to more efficacious analgesic strategies.

Previous human genetic association studies and transcriptomic analysis of chronic LBP have been performed using candidate gene and genome-wide approaches, and they have provided evidence for the involvement of a variety of genes in many biological pathways (*7*–*11*). Increasing evidence suggests that the pathophysiology of chronic pain involves a complex interplay between the nervous and immune systems; that is, chronic pain is a neuroinflammatory disorder mediated by neuronal and non-neuronal cells alike (*12*). Circulating immune cells such as neutrophils, monocytes, and T cells are recruited to sites of tissue damage and/or inflammation and often also infiltrate the peripheral and central nervous systems (*13*, *14*). Activation of these cells results in the expression of various inflammatory mediators, including cytokines/chemokines, lipids, and proteases, that act both directly on peripheral sensory or central second order neurons and indirectly on other immune or local cells to regulate pain. Microglia and astrocytes in the central nervous system act in a similar fashion, contributing to central sensitization and pain (*15*–*18*). The presence of these activated immune cells and glia, peripherally or centrally, is thought to contribute to the transition from acute to chronic pain (*19*–*21*).

Here, we used transcriptome-wide data to investigate the molecular pathophysiological mechanisms in peripheral blood immune cells at the transcriptome-wide level that underlie the transition of acute to chronic LBP, and we identified the protective effect of acute inflammatory responses against the development of chronic pain. We replicated our finding in an independent cohort of patients with another musculoskeletal pain condition, temporomandibular disorder (TMD). We then used rodent pain models to elucidate the mechanism mediating the transition from acute to chronic pain. Last, we

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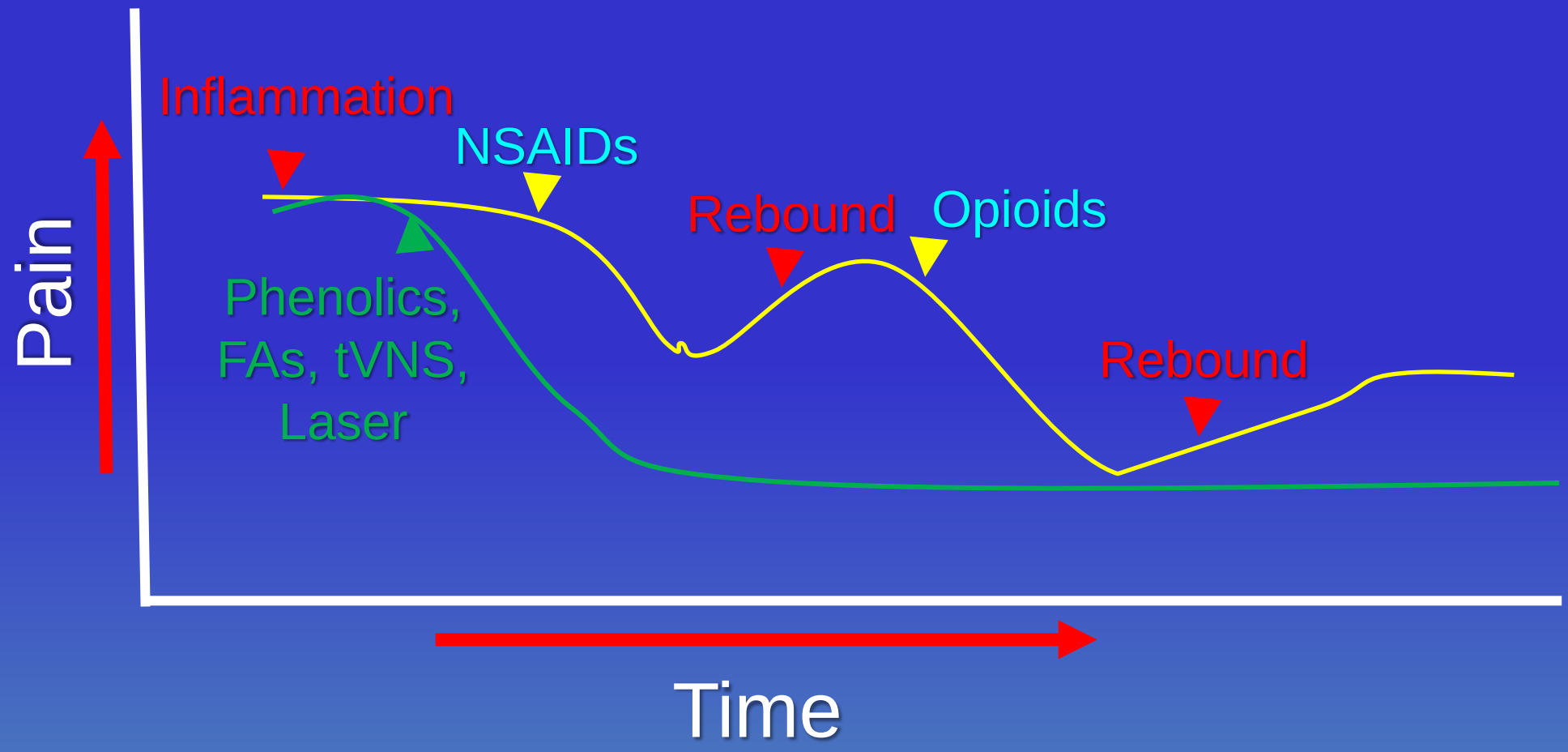
*Corresponding author. Email: luda.diatchenko@mcgill.ca (L.D.); allegri@italianpaingroup.com (M.A); jeffrey.mogil@mcgill.ca (J.S.M.)
†These authors contributed equally to this work.

Inflammatory/Pain Control



Rethinking Inflammation and Our Patients

The typical chiropractic patient today is more inflamed than the were 20-30 years ago. Care concepts have been slower to adapt to that reality.

“Indeed, chronic inflammatory diseases have been recognized as the most significant cause of death in the world today, with more than 50% of all deaths being attributable to inflammation-related diseases such as ischemic heart disease, stroke, cancer, diabetes mellitus, chronic kidney disease, non-alcoholic fatty liver disease (NAFLD) and autoimmune and neurodegenerative conditions.”

Furman et al. CHRONIC INFLAMMATION IN THE ETIOLOGY OF DISEASE ACROSS THE LIFE SPAN. Nature Medicine, 2019;25:1822–1832.

SPECIAL REPORT

A Potential Decline in Life Expectancy in the United States in the 21st Century

S. Jay Olshansky, Ph.D., Douglas J. Passaro, M.D., Ronald C. Hershow, M.D., Jennifer Layden, M.P.H., Bruce A. Carnes, Ph.D., Jacob Brody, M.D., Leonard Hayflick, Ph.D., Robert N. Butler, M.D., David B. Allison, Ph.D., and David S. Ludwig, M.D., Ph.D.

SUMMARY

Forecasts of life expectancy are an important component of public policy that influence age-based entitlement programs such as Social Security and Medicare. Although the Social Security Administration recently raised its estimates of how long Americans are going to live in the 21st century, current trends in obesity in the United States suggest that these estimates may not be accurate. From our analysis of the effect of obesity on longevity, we conclude that the steady rise in life expectancy during the past two centuries may soon come to an end.

The trend in the life expectancy of humans during the past thousand years has been characterized by a slow, steady increase[1,2] — a pattern frequently punctuated by a volatility in death rates caused by epidemics and pandemic infectious diseases, famines, and war.[3,4] This volatility was dramatically curtailed in the mid-19th century as infectious diseases yielded swiftly to improved living conditions, advances in public health, and medical interventions. During the past 30 years, the rise in life expectancy at birth in the United States decelerated relative to this historical pattern, and gains in life expectancy at older ages are now much smaller than they were in previous decades.[5]

How much higher can life expectancy rise? This is not just an academic question. The answer formulated today will have substantial influence on the rate at which taxes are levied and on the potential solvency of age-entitlement programs. Some scientists answer this question by extrapolating from historical trends, which has led to the recent prediction that life expectancy at birth will rise to 100 years in the United States and other developed nations by the year 2060.[6] The United Nations used a similar method but different assumptions to arrive at a projected life expectancy of 100 years for males and females in most countries by the year 2300.[7] The Social Security Administration (SSA) arrived at a more tempered but still optimistic view that life expectancy in the United States will continue its steady increases, reaching the mid-80s later in this century.[8]

A recently convened panel of advisers,[9] and some mathematical demographers who advocate the use of extrapolation,[10] have advised the SSA to project an even more rapid rate of increase in life expectancy for the U.S. population beyond that already anticipated between now and the latter part of this century. The bases for this advice include a demonstration that the maximum life span in Sweden has increased since the mid-19th century,[11] the world record for life expectancy at birth in developed nations has been increasing by three months per year since 1850, mortality declines occurred at older ages in the Group of Seven industrialized nations during the latter half of the 20th century,[12] and the prediction that "negligible senescence" will be scientifically engineered for humans in this century.[13] Negligible senescence is defined as age-specific mortality rates that remain constant throughout life as opposed to rising exponentially after puberty, which is common among humans and most other animals. This last point is important because it is the only "biologic" justification offered for the decision to raise forecasts of life expectancy.

Life-extending technology that might lead to much higher life expectancies does not yet exist and, should it be developed, must be widely implemented before it would influence statistics on population levels. We believe that potential forms of technology do not justify developing or revising forecasts of life expectancy. Extrapolation models fail to consider the health status of people currently

CDC Centers for Disease Control and Prevention

National Center for Health Statistics

Life Expectancy in the U.S. Dropped for the Second Year in a Row in 2021

For Immediate Release: August 31, 2022

Contact: CDC, National Center for Health Statistics, Office of Communication (301) 458-4800
E-mail: paoquery@cdc.gov

Life expectancy at birth in the United States declined nearly a year from 2020 to 2021, according to new provisional data from the CDC's National Center for Health Statistics (NCHS). That decline – 77.0 to 76.1 years – took U.S. life expectancy at birth to its lowest level since 1996. The 0.9 year drop in life expectancy in 2021, along with a 1.8 year drop in 2020, was the biggest two-year decline in life expectancy since 1921-1923.

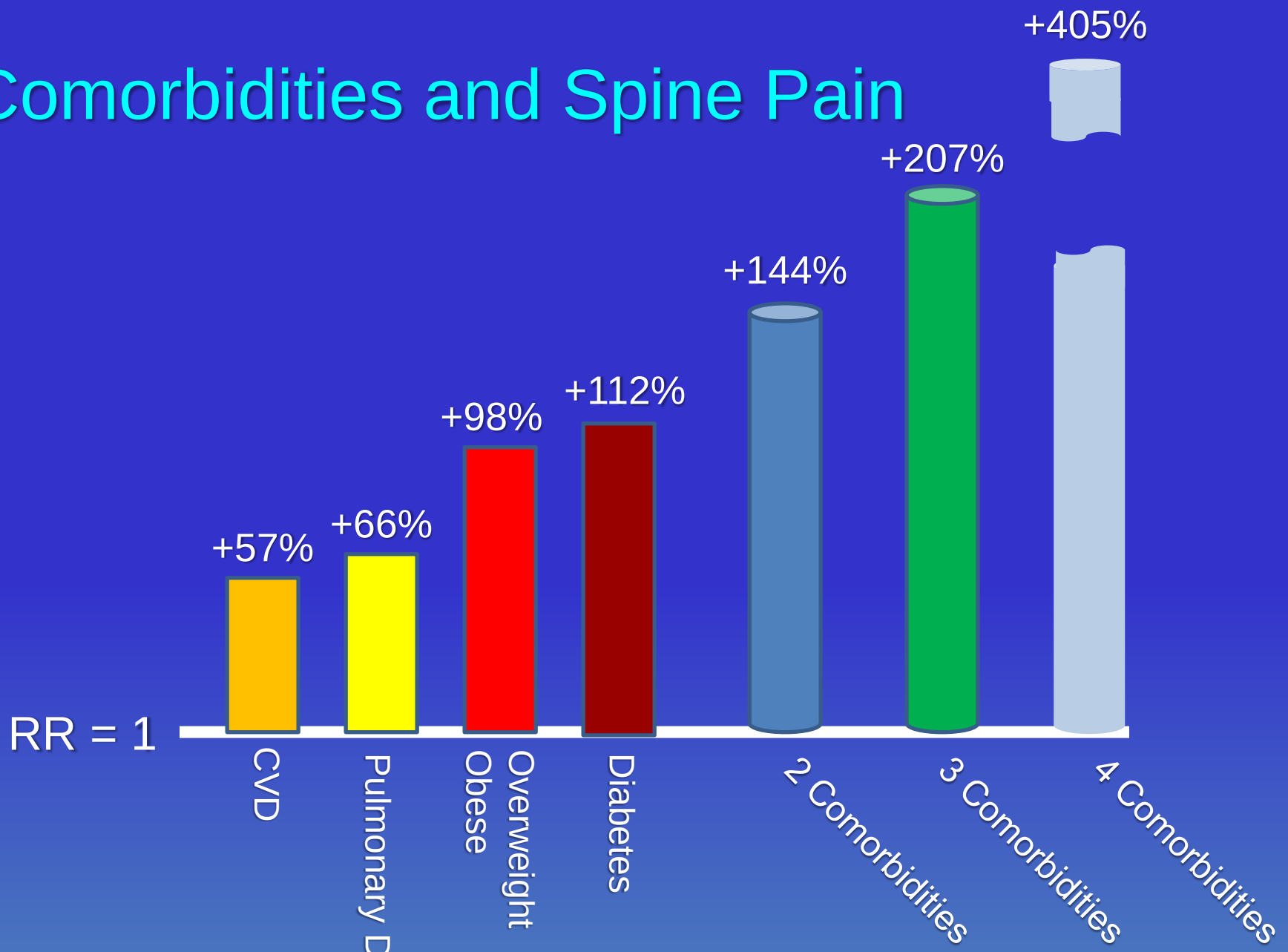
The data are featured in a new report, "Provisional Life Expectancy Estimates for 2021." The report shows non-Hispanic American Indian-Alaskan Native people (AIAN) had the biggest drop in life expectancy in 2021 – 1.9 years. AIAN people had a life expectancy at birth of 65.2 years in 2021 – equal to the life expectancy of the total U.S. population in 1944. AIAN life expectancy has declined 6.6 years from 2019 to 2021.

Non-Hispanic white people in the United States had the second biggest decline in life expectancy in 2021 – one full year from 77.4 in 2020 to 76.4 in 2021. Non-Hispanic Black people had the third biggest decline, a 0.7 year drop from 71.5 years in 2020 to 70.8 in 2021. Life expectancy at birth in 2021 was the lowest for both groups since 1995. After a large (4.0 year) drop in life expectancy from 2019 to 2020, Hispanic people in the U.S. had a slight decline in 2021 of 0.2 years to 77.6 years. Life expectancy for non-Hispanic Asian people also dropped slightly in 2021 – 0.1 years – to 83.5 years, the highest life expectancy of any race/ethnic group included in this analysis.

Other findings documented in the report:

- Life expectancy at birth for women in the United States dropped 0.8 years from 79.9 years in 2020 to 79.1 in 2021, while life expectancy for men dropped one full year, from 74.2 years in 2020 to 73.2 in 2021. The report shows the disparity in life expectancy between men and women grew in 2021 from 5.7 years in 2020 to 5.9 years in 2021. From 2000 to 2010, this disparity had narrowed to 4.8 years, but gradually increased from 2010 to 2019 and is now the largest gap since 1996.
- The declines in life expectancy since 2019 are largely driven by the pandemic. COVID-19 deaths contributed to nearly three-fourths or 74% of the decline from 2019 to 2020 and 50% of the decline from 2020 to 2021. An estimated 16% of the decline in life expectancy from 2020 to 2021 can be attributed to increases in deaths from accidents/unintentional injuries. Drug overdose deaths account for nearly half of all unintentional injury deaths. The most recent data reported by NCHS showed more than 109,000 overdose deaths in the one-year period ending in March of 2022.
- Other causes of death contributing to the decline in life expectancy from 2020 to 2021 include heart disease (4.1% of the decline), chronic liver disease and cirrhosis (3.0%), and suicide (2.1%). For men, the one-year decline in life

Comorbidities and Spine Pain



Inflammatory Aspects of Diet

High refined carbohydrate and sugar diet

Imbalanced omega-6 to Omega-3 intake

High saturated fat diet

Low phenol diet

The Food/Obesity/Inflammatory Relationships

1990s – Adipose tissue produces inflammatory cytokines

2000s – Circulating inflammatory markers are higher in obese persons versus matched normal weight controls.

2000s – Many foods/nutrients influence the inflammatory process as well as obesity risk.

Calder P. DIETARY FACTORS AND LOW-GRADE INFLAMMATION IN RELATION TO OVERWEIGHT AND OBESITY REVISITED. British Journal of Nutrition, 2022;127:1455-1457.

PubMed Citations

Years covered	Obesity AND inflammation
1980–1989	65
1990–1999	159
2000–2009	3961
2010–2019	19 801
2020-now	7433

The Food/Obesity/Inflammatory Relationships

“The phenomenon of post-prandial inflammation is described: both high simple sugar and high fat meals induce a elevated inflammation in the hours following consumption, and there is a view that this is part of the link between poor quality diets and the risk of non-communicable diseases.”

“Inclusion of fiber, some plant polyphenolic compounds or omega-3 fatty acids, among others, in the meal can mitigate its effects on inflammation.”

Calder P. DIETARY FACTORS AND LOW-GRADE INFLAMMATION IN RELATION TO OVERWEIGHT AND OBESITY REVISITED. British Journal of Nutrition, 2022;127:1455-1457.

The Insulin Resistance Cycle

Dietary Sugars and Carbs

Blood Glucose

Insulin

Muscle Cells, Liver, Pancreas

Triglycerides VLDL C

Insulin

White Adipose (Storage)

Decreased HDL

*Trig/HDL >2.5**

NAFLD

Small Particle LDL VLDL

Cytokines

Inflammation, Hormonal Dysfunction

*sensitivity=88%, specificity=72%

Sugar-Sweetened Beverage Consumption and Plasma Lipoprotein Cholesterol, Apolipoprotein, and Lipoprotein Particle Size Concentrations in US Adults

Danielle E Haslam,[1,2,3] Daniel I Chasman,[4] Gina M Peloso,[5] Mark A Herman,[6] Josée Dupuis,[5,7] Alice H Lichtenstein,[8] Caren E Smith,[9] Paul M Ridker,[4,10] Paul F Jacques,[1] Samia Mora,[4,10] and Nicola M McKeown[11]

[1]Nutritional Epidemiology Program, Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA; [2]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [3]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA; [4]Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA;

risk factors.

Results: SSB consumption was positively associated with LDL cholesterol, apoB, TG, RLP-TG, RLP-C, and non–HDL cholesterol concentrations and total cholesterol:HDL cholesterol and apoB:apoA1 ratios; and negatively associated with HDL cholesterol and apoA1 concentrations (*P*-trend range: <0.0001 to 0.008). After adjustment for traditional lipoprotein risk factors, SSB consumers had smaller LDL-P and HDL-P sizes; lower concentrations of large LDL-Ps and medium HDL-Ps; and higher concentrations of small LDL-Ps, small HDL-Ps, and large TRL-Ps (*P*-trend range: <0.0001 to 0.001).

Conclusions: Higher SSB consumption was associated with multiple emerging features of dyslipidemia that have been linked to higher cardiometabolic risk in US adults. *J Nutr* 2022;00:1–12.

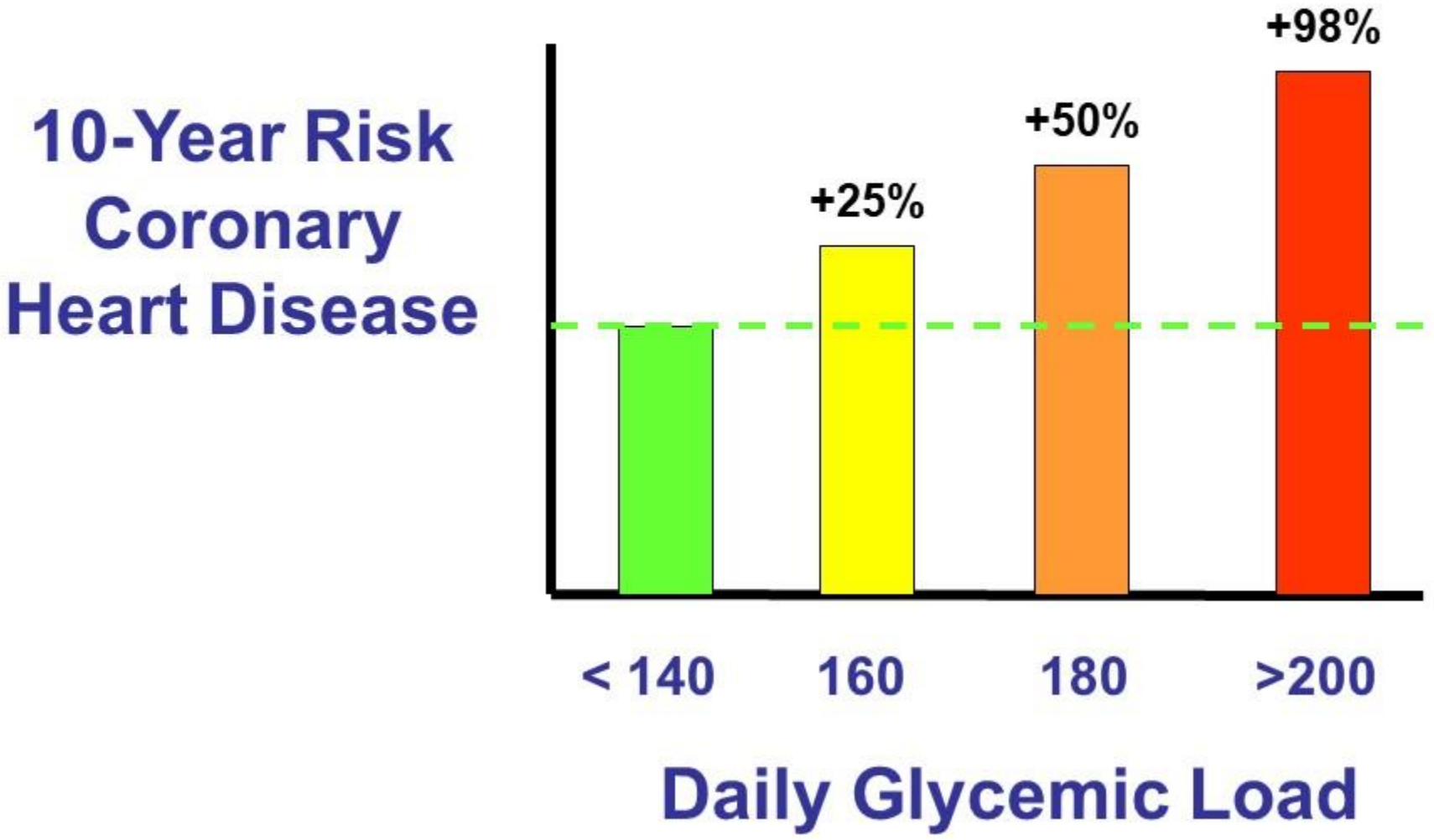
(apoB), HDL cholesterol, apolipoprotein A1 (apoA1), triglyceride (TG), and non–HDL cholesterol, as well as total cholesterol:HDL cholesterol ratio and apoB:apoA1 ratio, were quantified in both cohorts; concentrations of apolipoprotein E, apolipoprotein C3, RLP-TG, and RLP cholesterol (RLP-C) were measured in the FOS only. Lipoprotein particle sizes were calculated from nuclear magnetic resonance signals for lipoprotein particle subclass concentrations (TG-rich lipoprotein particles [TRL-Ps]: very large, large, medium, small, and very small; LDL particles [LDL-Ps]: large, medium, and small; HDL particles [HDL-Ps]: large, medium, and small). SSB consumption was estimated from food frequency questionnaire data. We examined the associations between SSB consumption and all lipoprotein and apoprotein measures in linear regression models, adjusting for confounding factors such as lifestyle, diet, and traditional lipoprotein risk factors.

Results: SSB consumption was positively associated with LDL cholesterol, apoB, TG, RLP-TG, RLP-C, and non–HDL cholesterol concentrations and total cholesterol:HDL cholesterol and apoB:apoA1 ratios; and negatively associated with HDL cholesterol and apoA1 concentrations (*P*-trend range: <0.0001 to 0.008). After adjustment for traditional lipoprotein risk factors, SSB consumers had smaller LDL-P and HDL-P sizes; lower concentrations of large LDL-Ps and medium HDL-Ps; and higher concentrations of small LDL-Ps, small HDL-Ps, and large TRL-Ps (*P*-trend range: <0.0001 to 0.001).

Conclusions: Higher SSB consumption was associated with multiple emerging features of dyslipidemia that have been linked to higher cardiometabolic risk in US adults. *J Nutr* 2022;00:1–12.

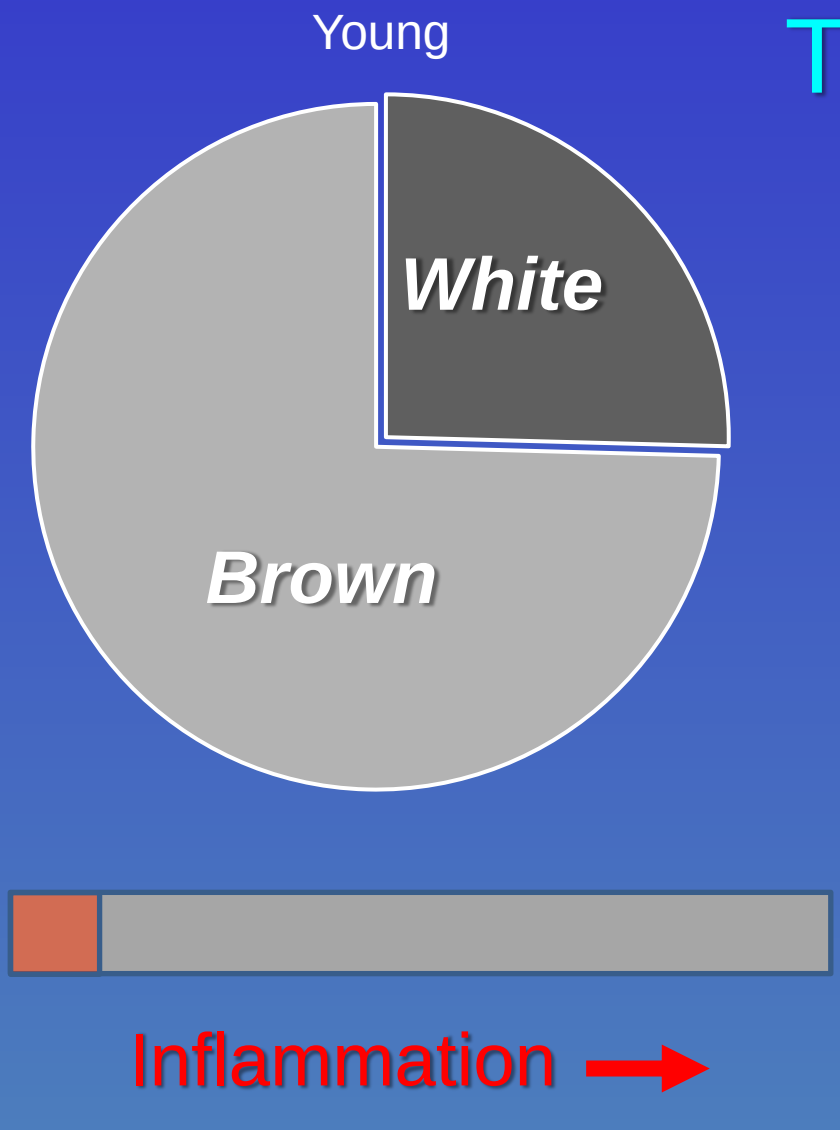
Keywords: carbohydrates, sugar-sweetened beverages, observational study, nutrition, lipoprotein particle size, diabetes, dyslipidemia, lipoproteins

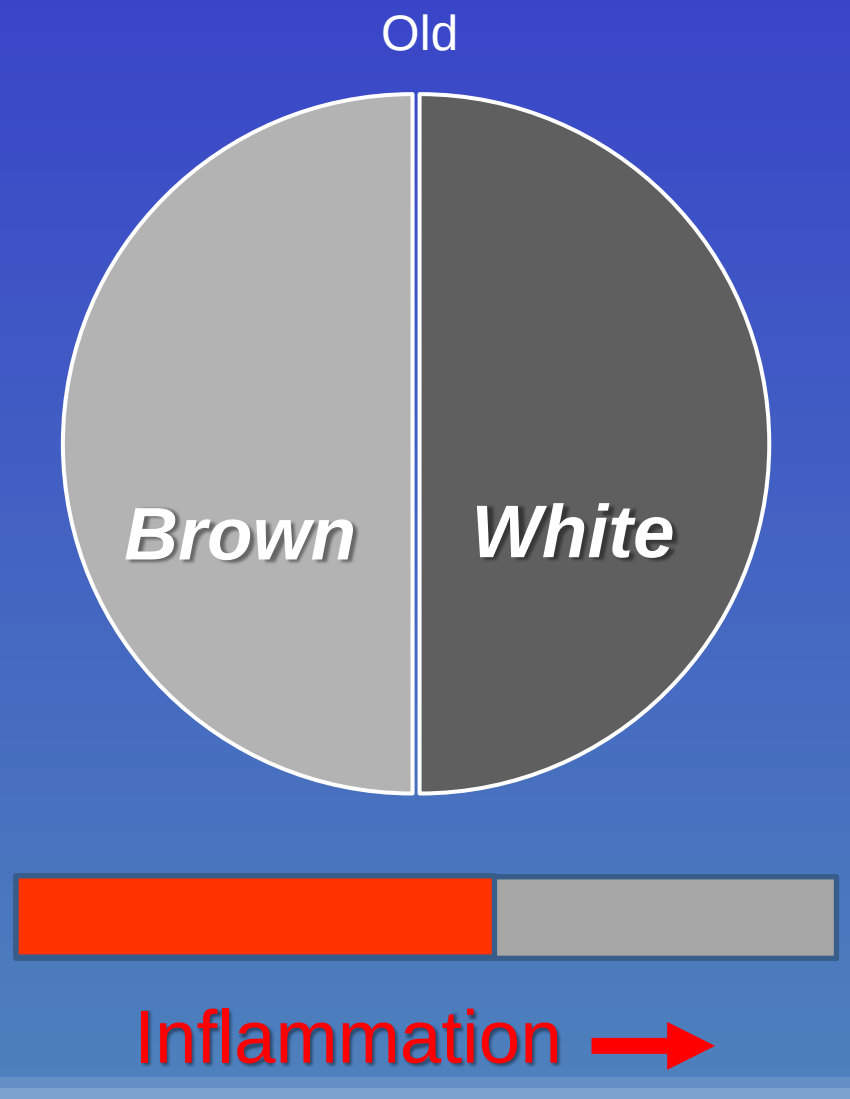
Refined Carbohydrates and Coronary Heart Disease Risk



American Journal of Clinical Nutrition - 2000

Age Related Adipose Tissue Shift





The Insulin Resistance Cascade

Too Little, Too Late

Central Fat increase	
Insulin increases	1-5 years
Atherogenic dyslipidemia	2-8 years
Pre-diabetic	5-10 years
Diabetic	10-15 years
Insulin dependent diabetic	15-20 years

Account Number	Patient ID	Control Number	Date and Time Collected	Date Reported	Sex	Age(Y/M/D)
45406935	DR – 59 YO F		04/07/09 01:36	04/08/09	F	59/06/24

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL
Potassium, Serum	4.8		mmol/L	3.5 - 5.2
Chloride, Serum	103		mmol/L	97 - 108
Carbon Dioxide, Total	31		mmol/L	20 - 32
Calcium, Serum	9.5		mg/dL	8.5 - 10.6
Protein, Total, Serum	6.7		g/dL	6.0 - 8.5
Albumin, Serum	4.3		g/dL	3.5 - 5.5
Globulin, Total	2.4		g/dL	1.5 - 4.5
A/G Ratio	1.8			1.1 - 2.5
Bilirubin, Total	0.3		mg/dL	0.1 - 1.2
Alkaline Phosphatase, S	68		IU/L	25 - 150
AST (SGOT)	16		IU/L	0 - 40
ALT (SGPT)	11		IU/L	0 - 40
Lipid Panel With LDL/HDL Ratio				
Cholesterol, Total	184		mg/dL	100 - 199
Triglycerides	**326**	**High**	mg/dL	0 - 149
HDL Cholesterol	**36**	**Low**	mg/dL	>39
Comment				
	According to ATP-III Guidelines, HDL-C >59 mg/dL is considered a negative risk factor for CHD.			
VLDL Cholesterol Cal	**65**	**High**	mg/dL	5 - 40
LDL Cholesterol Calc	83		mg/dL	0 - 99
LDL/HDL Ratio	2.3		ratio units	0.0 - 3.2
TSH	2.585		uIU/mL	0.450 - 4.500
C-Reactive Protein, Cardiac	**3.35**	**High**	mg/L	0.00 - 3.00
	Relative Risk for Future Cardiovascular Event			
			Low	<1.00
			Average	1.00 - 3.00
			High	>3.00
Hemoglobin A1c	5.4		%	<7.0
			Diabetic Adult	<7.0
			Healthy Adult	4.8 - 5.9
				(DCCT/NGSP)
	American Diabetes Association's Summary of Glycemic Recommendations for Adults with Diabetes: Hemoglobin A1c <7.0%. More stringent glycemic goals (A1c <6.0%) may further reduce complications at the cost of increased risk of hypoglycemia.			
Amylase, Serum	85		U/L	0 - 99
	Effective April 20, 2009, the reference interval for Amylase, Serum will be changing to:			31 -124

Non-HDL C = 148

Glycemic loads per serving		
Vegetables	1 -3	5
Fruits	3-10	2
Grains/starches	10-45	1
Snickers bar	*21.2*	*None!*
Coca Cola	*35.1*	

Summary Intake Report for [redacted]

Days Covered: 5 selected days between 8/20/2009 and 8/24/2009

Client Information

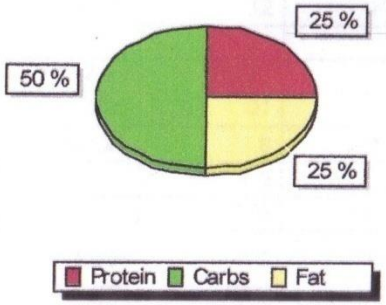
Start Date:	08/27/2009	**Starting Weight:**	180 pounds
Goal Date:	05/06/2010	**Desired Weight:**	162 pounds
Gender:	Male	**Desired Loss:**	18 pounds
Age:	48	**Starting Body Fat:**	N/A
Build:	Medium	**Desired Body Fat:**	N/A
Height:	71 in.	**Starting BMI:**	25.5
Activity Level:	Sedentary	**Desired BMI:**	22.9

Number of Intake Days: 5

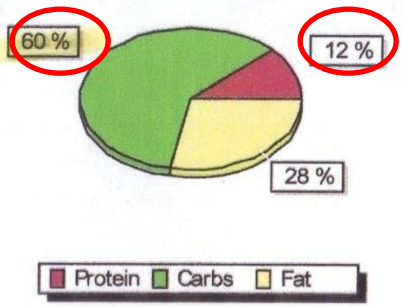
Average Calories Per Day: 2179 **Actual PCF Ratio:** 12-60-28

Daily Calorie Goal: 1863 **Desired PCF Ratio:** 25-50-25

Desired PCF Ratio



Actual PCF Ratio



Average Daily Intake Values

	Calories (kcal)	Protein (g)	Carbs (g)	Sugars (g)	Dietary Fiber (g)	Fat (g)	Sat fat (g)	Monounsat Fat (g)	Polyunsat Fat (g)	Omega-3 (g)
Breakfast	536.62	30.16	61.4	21.3	4.9	19.21	6.88	4.26	.8	.1
Morning Snack	121.49	1.51	15.27	1.35	.43	6.19	1.6	3.44	.79	.04
Lunch	519.77	13.8	90.5	61.15	2.42	13.35	4.27	2.9	1.25	.02
Afternoon Snack	85.33	1.07	13.33	7.47	.53	3.73	1.07			
Dinner	681.48	17.64	114.04	83.78	2.27	19.15	8.05	4.89	1.12	.03
Evening Snack	233.9	3.57	37.63	25.6	.77	8.1	3.12	.01		
Daily Total:	**2,178.6**	**67.74**	**332.17**	**200.65**	**11.32**	**69.73**	**24.98**	**15.49**	**3.95**	**.2**
Daily Goal:	**1,863**	**116.44**	**232.88**		**18.63**	**51.75**	**17.25**			
% of Daily Goal:	117 %	58 %	143 %	0 %	61 %	135 %	145 %	0 %	0 %	0 %

SUGAR : FIBER
= 17 : 1
IDEAL ≤ 1.5 : 1

MONO : SAT
0.6 : 1
IDEAL 4 : 1

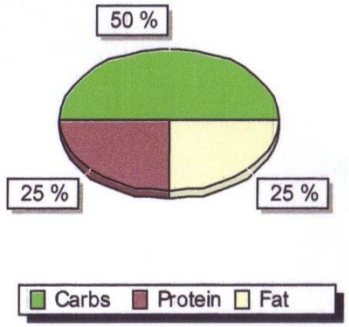
Detailed Intake Report for

Date:

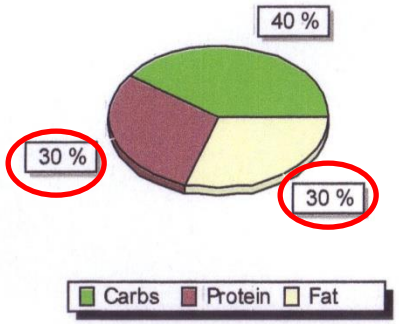
Client Information

Start Date:	01/22/2010	**Starting Weight:**	248 pounds
Goal Date:	04/28/2011	**Desired Weight:**	215 pounds
Gender:	Male	**Desired Loss:**	33 pounds
Age:	48	**Starting Body Fat:**	28.1%
Build:	Medium	**Desired Body Fat:**	17.1%
Height:	75 in.	**Starting BMI:**	31.4
Activity Level:	Sedentary	**Desired BMI:**	27.2
Actual Calories	1264	**Actual CPF Ratio:**	40-30-30
Daily Calorie Goal:	2433	**Desired CPF Ratio:**	50-25-25

Desired CPF Ratio



Actual CPF Ratio



Breakfast	Description	Serving Size	Gram Wt.	Calories (kcal)	Protein (g)	Carbs (g)	Sugars (g)	Dietary Fiber (g)
100% WHOLE GRAIN BREAD		1 slice	36	80	4	15	1	4
PEACH, RAW	4/lb (2.5" dia)	1 medium	98	38.22	.89	9.35	8.22	1.47
ALMOND BUTTER, NO SALT	plain	1 tbsp	16	101.28	2.41	3.4		.59
Meal Total:			150	219.5	7.31	27.74	9.22	6.06
Morning Snack								
APPLE W/SKIN, RAW	3/lb (2.75" dia)	1 medium	138	71.76	.36	19.06	14.34	3.31
ALMOND, RAW	23 whole kernels	1 oz	28	163.86	6.03	5.6	1.36	3.35
Meal Total:			166	235.62	6.39	24.65	15.7	6.66
Lunch								
CHICKEN BREAST, BONELESS	'Always Tender'	1 breast	161	150	29	2		
ASPARAGUS, BOILED	drained	1 cup	180	39.6	4.32	7.4	2.34	3.6
CAULIFLOWER, BOILED, NO SALT	drained (1" pieces)	1 cup	124	28.52	2.28	5.1	1.75	3.35
Meal Total:			465	218.12	35.6	14.49	4.09	6.95

Detailed Intake Report fo [redacted] ntinued)

Afternoon Snack	Description	Serving Size	Gram Wt.	Calories (kcal)	Protein (g)	Carbs (g)	Sugars (g)	Dietary Fiber (g)
HUMMUS, RAW, HP (SEASONED MASHED CHICKPEAS)		2 tbsp	30	53.1	1.46	6.04	.14	1.2
CAULIFLOWER, RAW		1 cup	100	25	1.98	5.3	2.4	2.5
Meal Total:			130	78.1	3.44	11.34	2.54	3.7
Dinner								
SALMON, ATLANTIC, WILD, COOKED	dry heat	4 oz	113	206.27	28.83			
LIMA BEAN, LARGE, BOILED, NO ADDED SALT	mature seeds	1 cup	188	216.2	14.66	39.25	5.45	13.16
SNAP BEAN, BOILED, NO ADDED SALT (GREEN BEAN)	drained	1 cup	125	43.75	2.36	9.85	1.94	4
Meal Total:			426	466.22	45.86	49.1	7.39	17.16
Evening Snack								
HUMMUS, RAW, HP (SEASONED MASHED CHICKPEAS)		1 tbsp	15	26.55	.73	3.02	.07	.6
BROCCOLI FLOWER CLUSTERS, RAW	flowerets	1 cup	71	19.88	2.12	3.72		
Meal Total:			86	46.43	2.85	6.74	.07	.6
Daily Total:			1,424	1,263.99	101.43	134.07	39.01	41.13
Daily Goal:				2,433	152.06	304.13		24.33
% of Daily Goal:				52 %	67 %	44 %		169 %

Breakfast	Fat (g)	Sat fat (g)	Monounsat Fat (g)	Polyunsat Fat (g)	Omega-3 (g)	Omega-6 (g)	Cholest (mg)	Alcohol (g)	Sodium (mg)	
100% WHOLE GRAIN BREAD	1.5								90	
PEACH, RAW	.24	.02	.07	.08	.00	.08				
ALMOND BUTTER, NO SALT	9.46	.9	6.14	1.98					1.76	
Meal Total:	**11.2**	**.91**	**6.21**	**2.07**	**.00**	**.08**			**91.76**	
Morning Snack										
APPLE W/SKIN, RAW	.23	.04	.01	.07	.01	.06			1.38	
ALMOND, RAW	14.36	1.1	9.12	3.46		3.46			.28	
Meal Total:	**14.59**	**1.14**	**9.13**	**3.53**	**.01**	**3.52**			**1.66**	

Date and Time Collected	Date Entered	Date and Time Reported	Physician Name	MRN	Physician ID
08/14/09 11:35	08/15/09	08/15/09 06:47ET			

DR – 59 YO

Tests Ordered
Comp. Metabolic Panel (14); Lipid Panel With LDL/HDL Ratio; C-Reactive Protein, Cardiac

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL
Comp. Metabolic Panel (14)				
Glucose, Serum	98		mg/dL	65 - 99
BUN	15		mg/dL	5 - 26
Creatinine, Serum	0.93		mg/dL	0.57 - 1.00
eGFR	>59		mL/min/1.73	>59
eGFR AfricanAmerican	>59		mL/min/1.73	>59
Note: Persistent reduction for 3 months or more in an eGFR <60 mL/min/1.73 m2 defines CKD. Patients with eGFR values >/=60 mL/min/1.73 m2 may also have CKD if evidence of persistent proteinuria is present. Additional information may be found at www.kdoqi.org.				
BUN/Creatinine Ratio	16			8 - 27
Sodium, Serum	144		mmol/L	135 - 145
Potassium, Serum	5.3	High	mmol/L	3.5 - 5.2
Chloride, Serum	104		mmol/L	97 - 108
Carbon Dioxide, Total	29		mmol/L	20 - 32
Calcium, Serum	10.0		mg/dL	8.5 - 10.5
Protein, Total, Serum	7.1		g/dL	6.0 - 8.5
Albumin, Serum	4.4		g/dL	3.5 - 5.5
Globulin, Total	2.7		g/dL	1.5 - 4.5
A/G Ratio	1.6			1.1 - 2.5
Bilirubin, Total	0.4		mg/dL	0.1 - 1.2
Alkaline Phosphatase, S	61		IU/L	25 - 150
AST (SGOT)	19		IU/L	0 - 40
ALT (SGPT)	21		IU/L	0 - 40
Lipid Panel With LDL/HDL Ratio				
Cholesterol, Total	184		mg/dL	100 - 199
Triglycerides	103		mg/dL	0 - 149
HDL Cholesterol	42		mg/dL	>39
Comment: According to ATP-III Guidelines, HDL-C >59 mg/dL is considered a negative risk factor for CHD.				
VLDL Cholesterol Cal	21		mg/dL	5 - 40
LDL Cholesterol Calc	121	High	mg/dL	0 - 99
LDL/HDL Ratio	2.9		ratio units	0.0 - 3.2

8-20-09

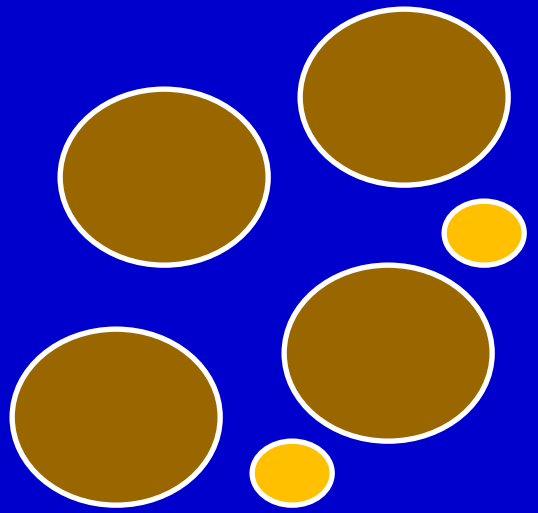
COM

for Dr Banks

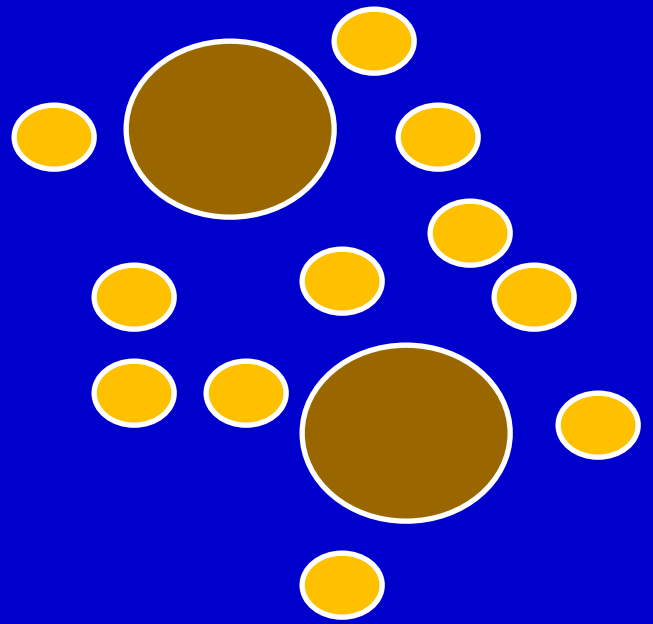
Trig/HDL 2.5:1

Non-HDL C = 142

LDL Cholesterol
125 mg/dL
Apo A1 Pattern

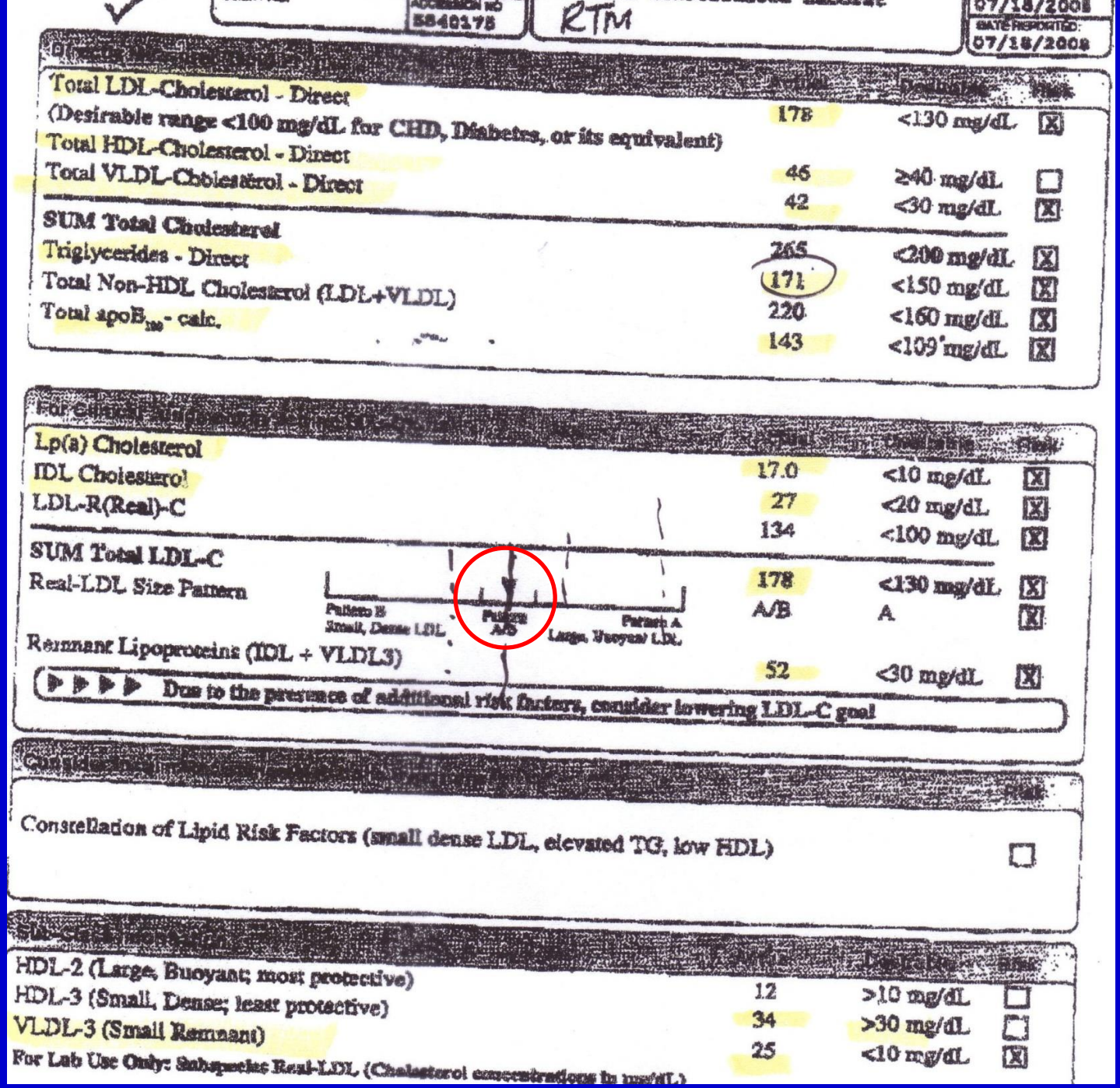


LDL Cholesterol
125 mg/dL
Apo B Pattern



Apo B

Apo A1



Total LDL-Cholesterol - Direct (Desirable range <100 mg/dL for CHD, Diabetes, or its equivalent)	178	<130 mg/dL	X
Total HDL-Cholesterol - Direct	46	≥40 mg/dL	
Total VLDL-Cholesterol - Direct	42	<30 mg/dL	X
SUM Total Cholesterol	265	<200 mg/dL	X
Triglycerides - Direct	171	<150 mg/dL	X
Total Non-HDL Cholesterol (LDL+VLDL)	220	<160 mg/dL	X
Total apoB$_{100}$ - calc.	143	<109 mg/dL	X
Lp(a) Cholesterol	17.0	<10 mg/dL	X
IDL Cholesterol	27	<20 mg/dL	X
LDL-R(Real)-C	134	<100 mg/dL	X
SUM Total LDL-C	178	<130 mg/dL	X
Real-LDL Size Pattern	A/B	A	X
Remnant Lipoproteins (IDL + VLDL3)	52	<30 mg/dL	X
Constellation of Lipid Risk Factors (small dense LDL, elevated TG, low HDL)			
HDL-2 (Large, Buoyant; most protective)	12	>10 mg/dL	
HDL-3 (Small, Dense; least protective)	34	>30 mg/dL	
VLDL-3 (Small Remnant)	25	<10 mg/dL	X

▶▶▶▶ Due to the presence of additional risk factors, consider lowering LDL-C goal

For Lab Use Only: Subspecies Real-LDL (Cholesterol concentrations in mg/dL)

LDL	178
VLDL	42
Atherogenic	220
Trig	171
HDL	46
Trig/HDL	3.7
Apo B	143

Date and Time Collected	Date Entered	Date and Time Reported			
02/27/09 15:26	02/27/09	03/04/09 05:42ET		NPI	19322

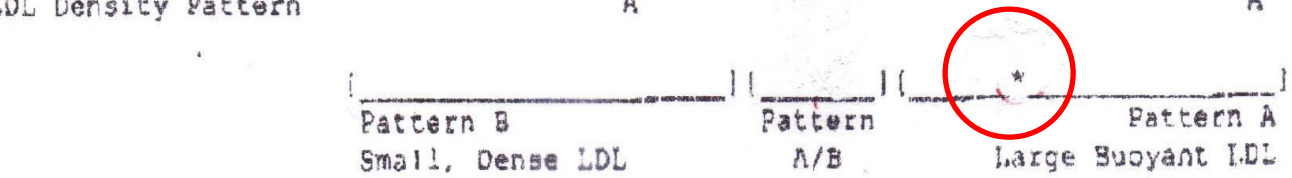
Tests Ordered

VAP Cholesterol Profile

General Comments

PID:

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL
VAP Cholesterol Profile				
Lipids				
LDL Cholesterol	**152**	**High**	mg/dL	<130
HDL Cholesterol	57		mg/dL	>=40
VLDL Cholesterol	25		mg/dL	<30
Cholesterol, Total	**234**	**High**	mg/dL	<200
Triglycerides	126		mg/dL	<150
Non HDL Chol. (LDL+VLDL)	**178**	**High**	mg/dL	<160
apoB100-calc	**116**	**High**	mg/dL	<109
LDL-R (Real)-C	**106**	**High**	mg/dL	<100
Lp(a) Cholesterol	**24.0**	**High**	mg/dL	<10
IDL Cholesterol	**22**	**High**	mg/dL	<20
Remnant Lipo. (IDL+VLDL3)	**38**	**High**	mg/dL	<30
Clinical Consideration				
Probable Metabolic Syndrome	No			No
Sub-Class Information				
HDL-2 (Most Protective)	17		mg/dL	>10
HDL-3 (Less Protective)	40		mg/dL	>30
VLDL-3 (Small Remnant)	**16**	**High**	mg/dL	<10
LDL1 Pattern A	19.1		mg/dL	
LDL2 Pattern A	31.0		mg/dL	
LDL3 Pattern B	48.6		mg/dL	
LDL4 Pattern B	7.3		mg/dL	
LDL Density Pattern	A			A



LDL	152
VLDL	25
Atherogenic	177
Trig	126
HDL	57
Trig/HDL	2.2
Apo B	116

Berberine in Type Two Diabetes

	BBR	Metformin	Rosiglitisone
FBG (Pre)	185	196	163
(Post)	137 (26%)	137 (30%)	135 (17%)
HbA1c	8.3	9.4	8.3
	6.8 (18%)	7.2 (23%)	6.8 (17%)
TG	150	150	168
	124 (18%)	142 (5%)	142 (16%)

From Zhang et al - Metab. Clin. Exp, 2009

Inflammatory Aspects of Diet

High refined carbohydrate and sugar diet

Imbalanced omega-6 to Omega-3 intake

High saturated fat diet

Low phenol diet

The Omega-3 and Omega-6 Fatty Acids and Inflammatory Resolution

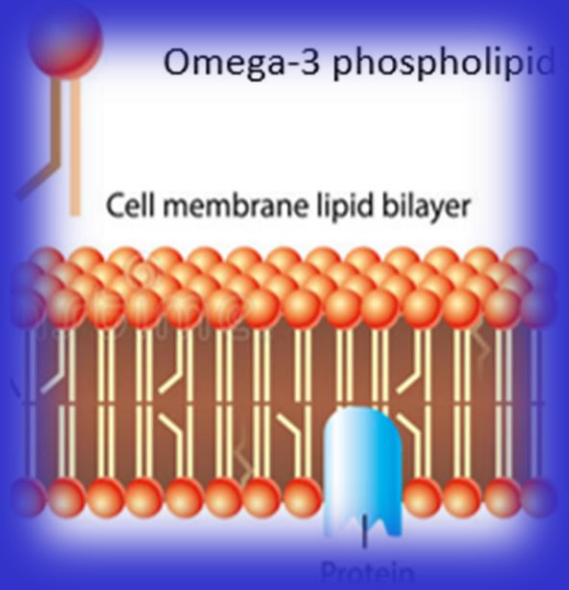
Our ancestral diet was though to contain > 6 grams of omega-3 FAs daily

It also contained an Omega-6 : Omega-3 ratio of +/- 2:1

Current EPA and DHA intake averages about 90 mgs daily with 1.5 grams of ALA.

Eat or supplement!

Cell membrane omega fatty acid balance

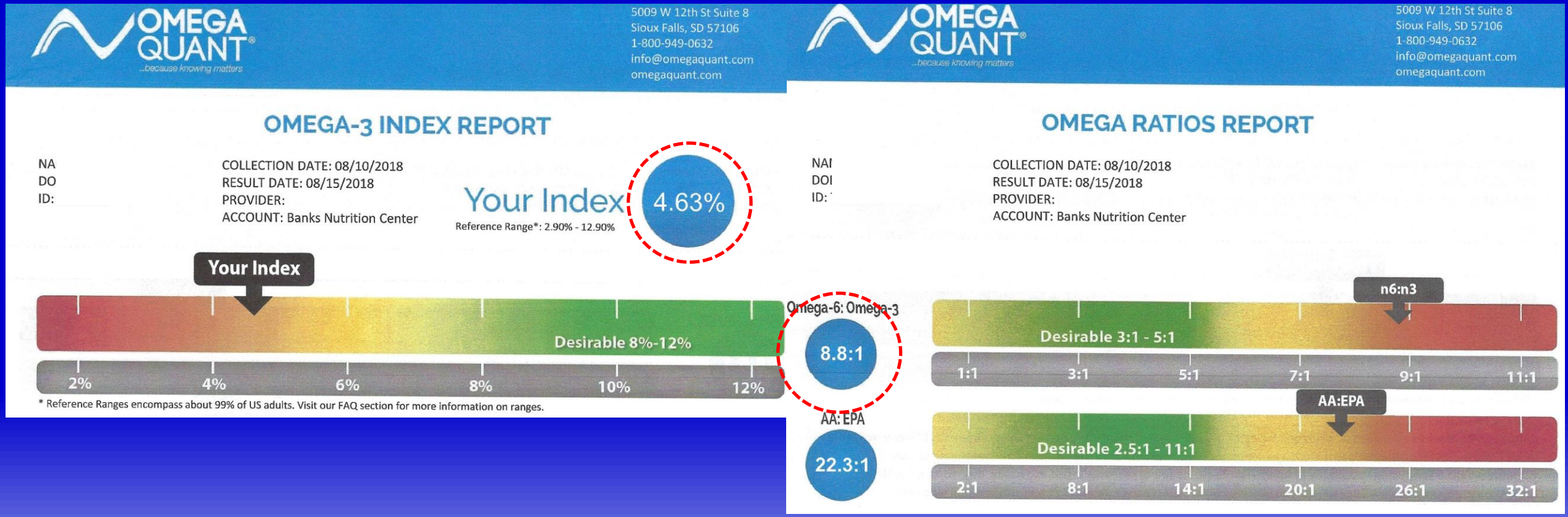


Both omega-6 and omega-3 fatty acids are needed for optimal inflammatory control.

The optimal omega-6:omega-3 is between 2:1 and 4:1.

Cell membrane measurements are important in optimizing omega FA balance.

What are the Omega-3 and Omega-6 Targets?



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OMEGA-3 INDEX REPORT

NA
DO
ID:

COLLECTION DATE: 08/10/2018
RESULT DATE: 08/15/2018
PROVIDER:
ACCOUNT: Banks Nutrition Center

Your Index 4.63%
Reference Range*: 2.90% - 12.90%

Your Index
Desirable 8%-12%
2% 4% 6% 8% 10% 12%

* Reference Ranges encompass about 99% of US adults. Visit our FAQ section for more information on ranges.

Omega-6: Omega-3
8.8:1

AA:EPA
22.3:1

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omegaquant.com

OMEGA RATIOS REPORT

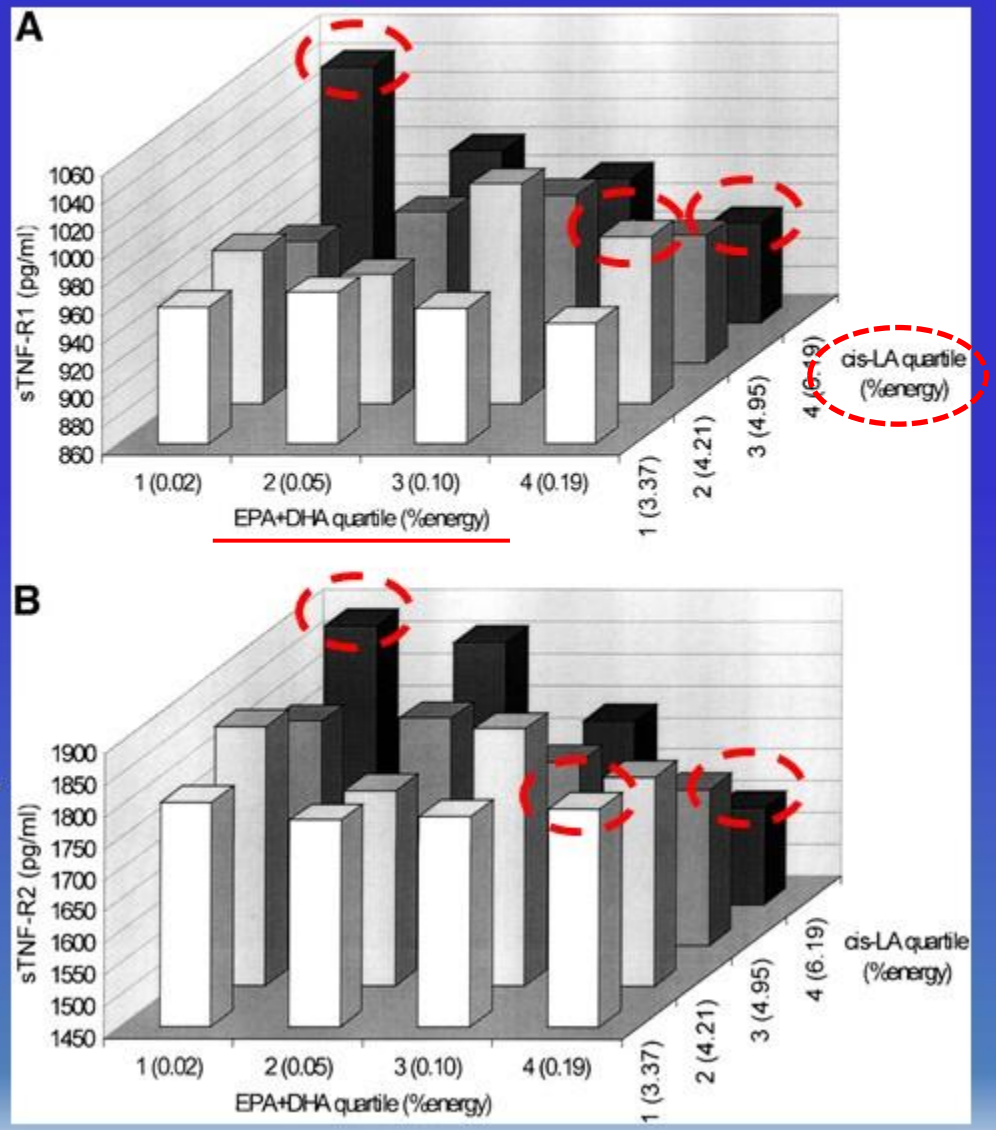
NAI
DOI
ID:

COLLECTION DATE: 08/10/2018
RESULT DATE: 08/15/2018
PROVIDER:
ACCOUNT: Banks Nutrition Center

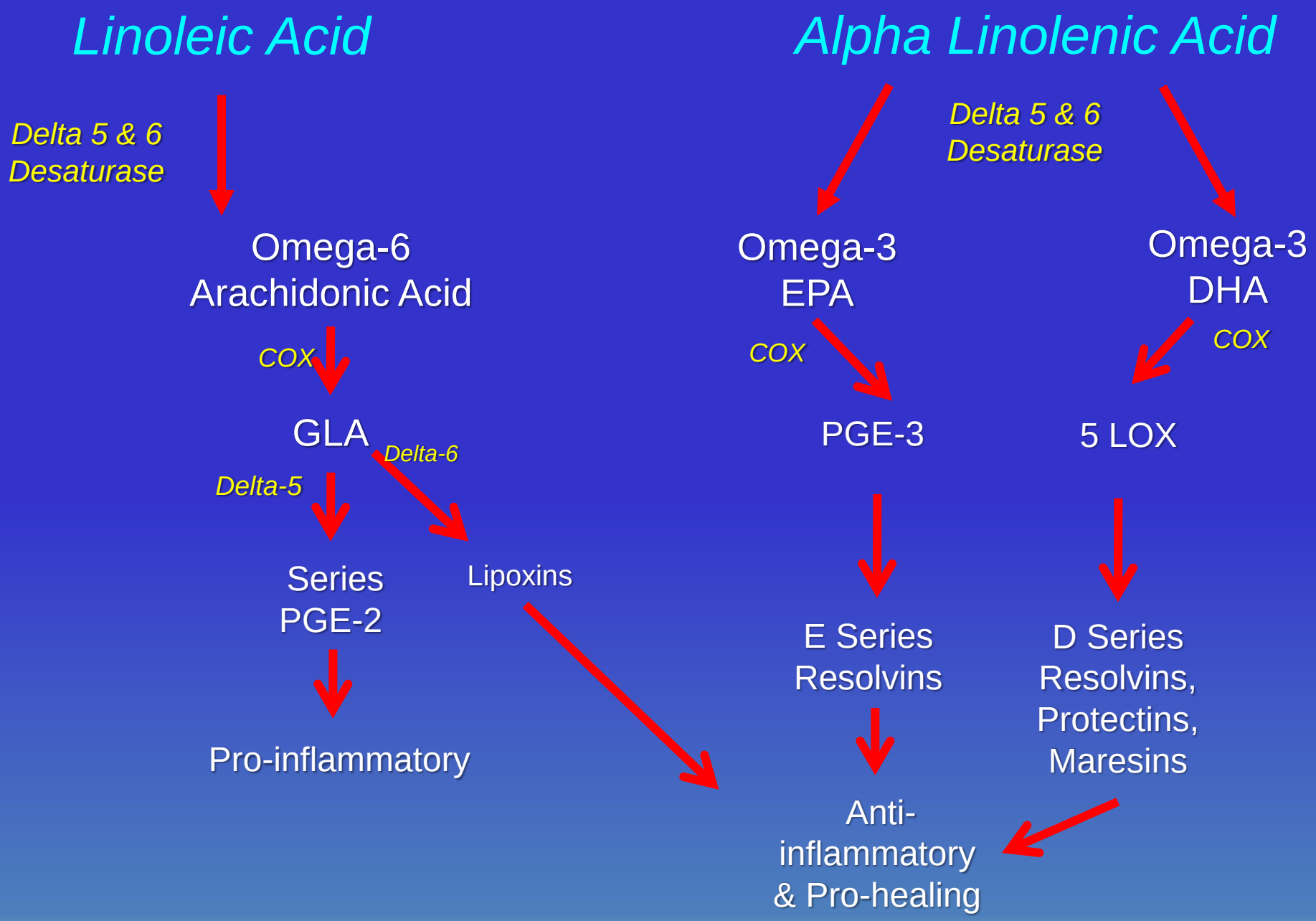
n6:n3
Desirable 3:1 - 5:1
1:1 3:1 5:1 7:1 9:1 11:1

AA:EPA
Desirable 2.5:1 - 11:1
2:1 8:1 14:1 20:1 26:1 32:1

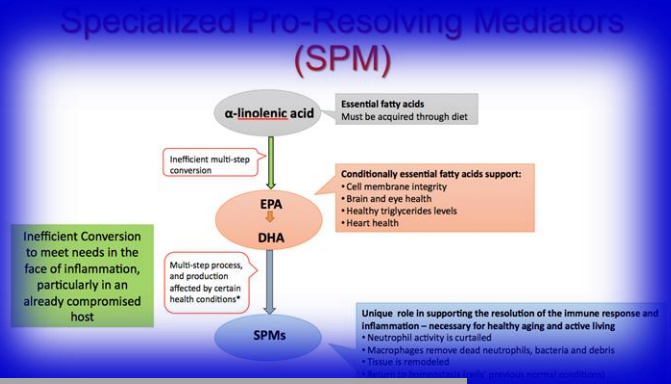
Plasma sTNF-R1 (A) and sTNF-R2 (B) levels in relation to quartiles of EPA+DHA and cis-LA intake



Pischon, T. et al. Circulation, 2003;108:155-160.


Linoleic Acid
Delta 5 & 6 Desaturase
Omega-6 Arachidonic Acid
COX
GLA
Delta-6
Delta-5
Series PGE-2
Pro-inflammatory
Lipoxins
Alpha Linolenic Acid
Delta 5 & 6 Desaturase
Omega-3 EPA
COX
PGE-3
E Series Resolvins
Omega-3 DHA
COX
5 LOX
D Series Resolvins, Protectins, Maresins
Anti-inflammatory & Pro-healing

•. 2022 Jun 9;14(12):2408
•. 2022 Jun 9;14(12):2408
•. 2022 Jun 9;14(12):2408



SASP, SPMs and Omega-3s

"In fully adjusted models, risk for incident AD in the highest RBC DHA quintile (Q5) was 49% lower compared with the lowest quintile (Q1) (Hazard ratio [HR]: 0.51, 95% confidence interval [CI]: 0.27, 0.96)."

Sala-Vila et al. Red Blood Cell DHA Is Inversely Associated with Risk of Incident Alzheimer's Disease and All-Cause Dementia: Framingham Offspring Study. Nutrients. 2022 Jun; 14(12): 2408.

Arnardottir et al. AGING DELAYS RESOLUTION OF ACUTE INFLAMMATION IN MICE: REPROGRAMMING THE HOST RESPONSE WITH NOVEL NANO-PRORESOLVING MEDICINES. J Immunol. 2014;193:4235-44.

Inflammatory Aspects of Diet

High refined carbohydrate and sugar diet

Imbalanced omega-6 to Omega-3 intake

High saturated fat diet

Low phenol diet

H

Cell Reports
Article

Saturated Fatty Acids Engage an IRE1α-Dependent Pathway to Activate the NLRP3 Inflammasome in Myeloid Cells

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[2]Biomedical Sciences Graduate Program
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http://dx.doi.org/10.1016/j.celrep.2016.02.053

SUMMARY

Diets rich in saturated fatty acids (SFAs) produce a form of tissue inflammation driven by "metabolically activated" macrophages. We show that SFAs, when in excess, induce a unique transcriptional signature in both mouse and human macrophages that is enriched by a subset of ER stress markers, particularly IRE1α and many adaptive downstream target genes. SFAs also activate the NLRP3 inflammasome in macrophages, resulting in IL-1β secretion. We found that IRE1α mediates SFA-induced IL-1β secretion by macrophages and that its activation by SFAs does not rely on unfolded protein sensing. We show instead that the ability of SFAs to stimulate either IRE1α activation or IL-1β secretion can be specifically reduced by preventing their flux into phosphatidylcholine (PC) or by increasing unsaturated PC levels. Thus, IRE1α is an unrecognized intracellular PC sensor critical to the process by which SFAs stimulate macrophages to secrete IL-1β, a driver of diet-induced tissue inflammation.

INTRODUCTION

Chronic consumption of diets rich in fat, particularly saturated fat, is associated with the accumulation of immune cells such as macrophages and dendritic cells in metabolic tissues like the white adipose. Subsets of these accumulating myeloid cells (MCs) express inflammatory markers and secrete pro-inflammatory cytokines that also comprise the response to lipopolysaccharide (LPS) stimulation (Lumeng et al., 2007; Weisberg et al., 2003), and targeting inflammatory pathways in these cell types has alleviated diet-induced insulin resistance in animal models (Yuan et al., 2001; Solinas et al., 2007). More recent work shows that adipose tissue macrophages (ATMs) from obese mice have a pattern of "metabolic activation" (M_{Me}) that is distinct from that induced by LPS (M_{LPS}) or other danger- and pathogen-associated molecular patterns (DAMPs and PAMPs; Xu et al., 2013; Kratz et al., 2014). However, the molecular details and functional consequences of M_{Me} polarization are poorly understood.

Treating cultured bone-marrow-derived macrophages or dendritic cells (BMDMs and BMDCs) with saturated fatty acids (SFAs) recapitulates many features of M_{Me} polarization that are seen in the ATMs of mice consuming diets high in saturated fat (Nguyen et al., 2007; Suganami et al., 2007; Kratz et al., 2014). These include not only the secretion of NF-κB-dependent M_{LPS} cytokines such as interleukin 6 (IL-6) and tumor necrosis factor (TNF) (Shi et al., 2006), but also activation of the NLRP3 inflammasome (Wen et al., 2011), an intracellular protein complex that assembles in response to DAMPs and PAMPs and catalyzes the cleavage and maturation of the cytokines IL-1β and IL-18.

Because circulating IL-1β levels are elevated in diet-induced obesity (DIO) and targeting IL-1β, its receptor, or components of the NLRP3 inflammasome protects obese mice from glucose intolerance and other metabolic consequences of DIO (Osborn et al., 2008; Stienstra et al., 2010; Wen et al., 2011), there is interest in understanding how SFAs activate the NLRP3 inflammasome. Prior studies have implicated reactive oxygen species accumulation due to impairment of AMPK-regulated autophagy in this process (Wen et al., 2011). Others have pointed to a stimulatory role for ceramide production (Schilling et al., 2013), but recent work suggests that de novo ceramide synthesis does not contribute to SFA-induced NLRP3 inflammasome activation (Camell et al., 2015). As such, the question remains unresolved.

SFA-treated MCs also display endoplasmic reticulum (ER) stress and activate the unfolded protein response (UPR), a key component of which is triggered by activation of the ER stress sensor inositol-requiring enzyme 1-alpha (IRE1α). Recognition of unfolded proteins in the ER lumen stimulates

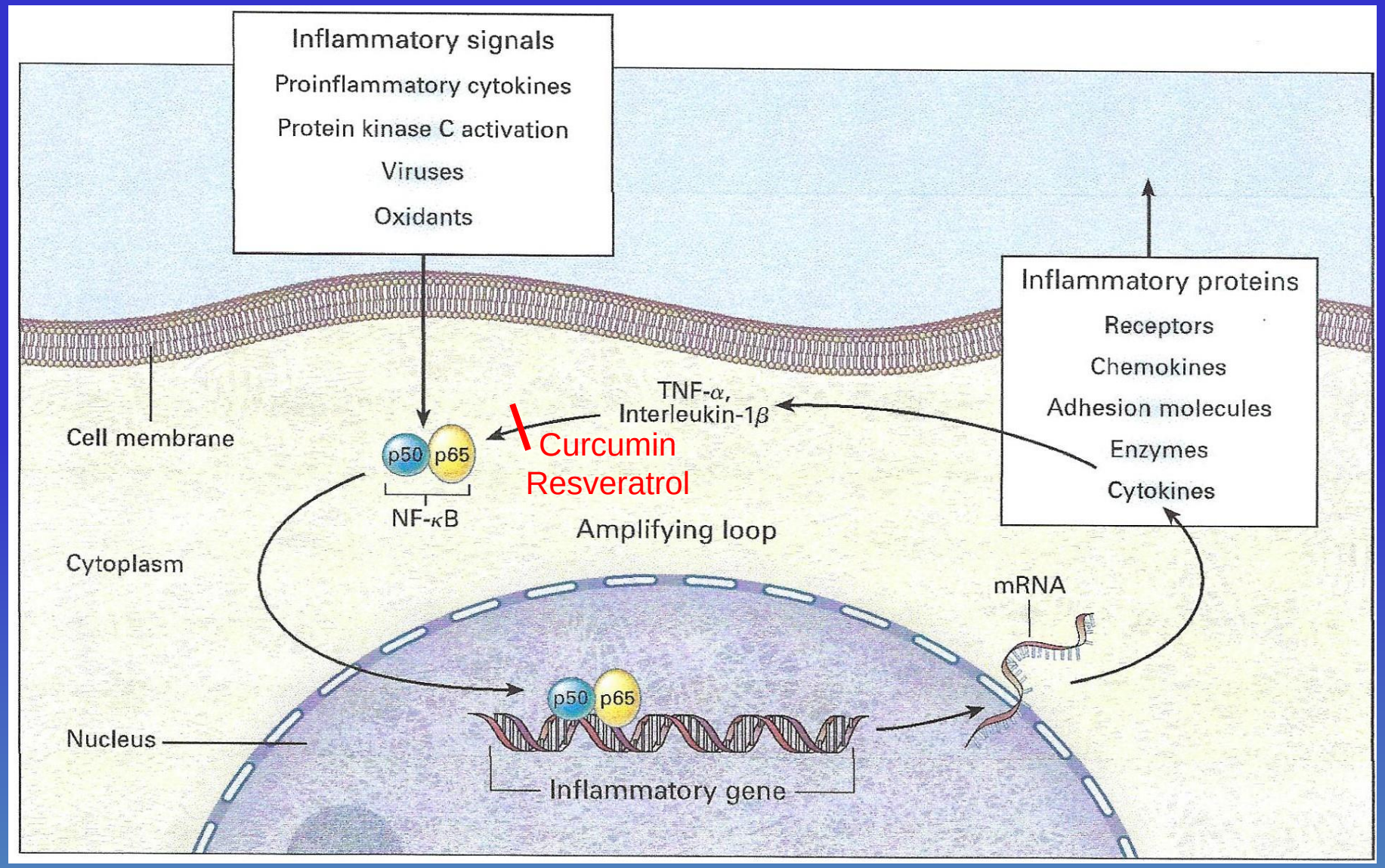
Inflammatory Aspects of Diet

High refined carbohydrate and sugar die

Imbalanced omega-6 to Omega-3 intake

High saturated fat diet

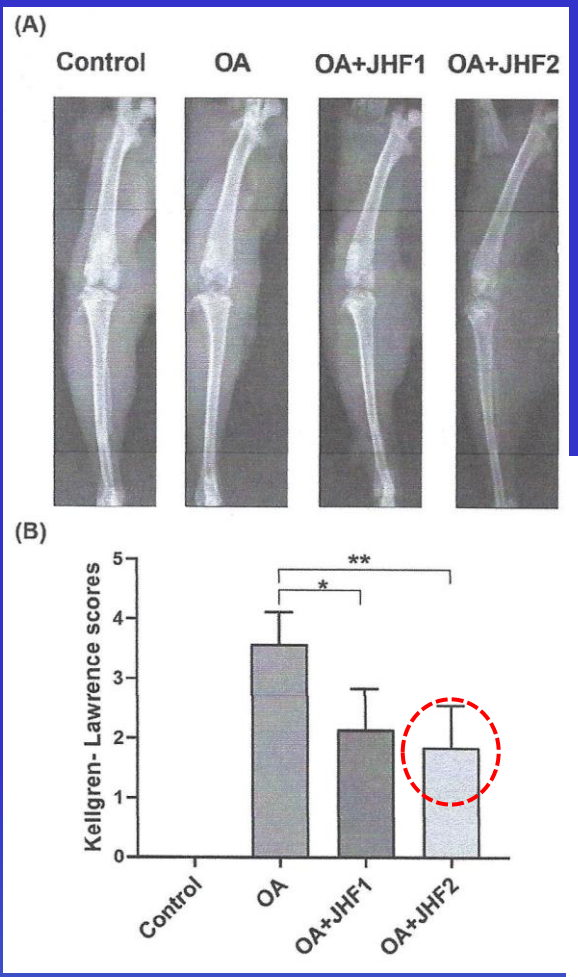
Low phenol diet

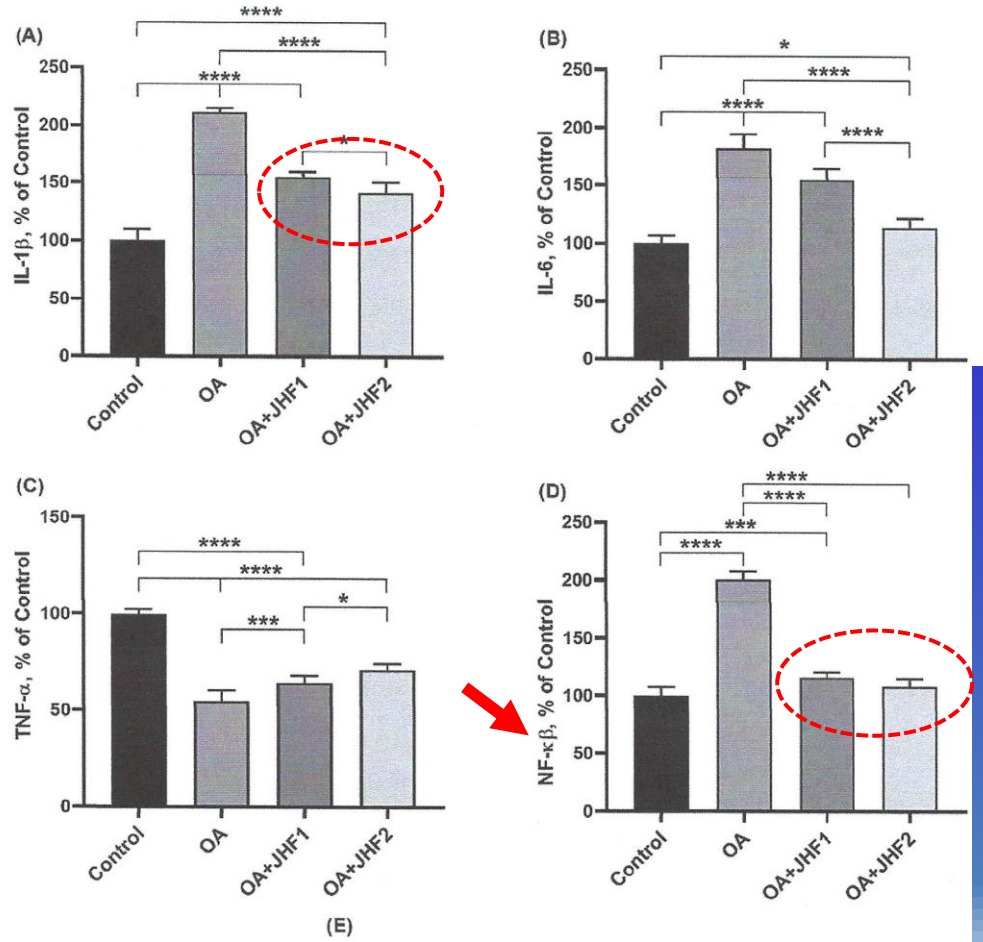

Inflammatory signals
Proinflammatory cytokines
Protein kinase C activation
Viruses
Oxidants
Inflammatory proteins
Receptors
Chemokines
Adhesion molecules
Enzymes
Cytokines
TNF-α,
Interleukin-1β
Cell membrane
p50
p65
Curcumin
Resveratrol
NF-κB
Amplifying loop
Cytoplasm
mRNA
p50
p65
Nucleus
Inflammatory gene

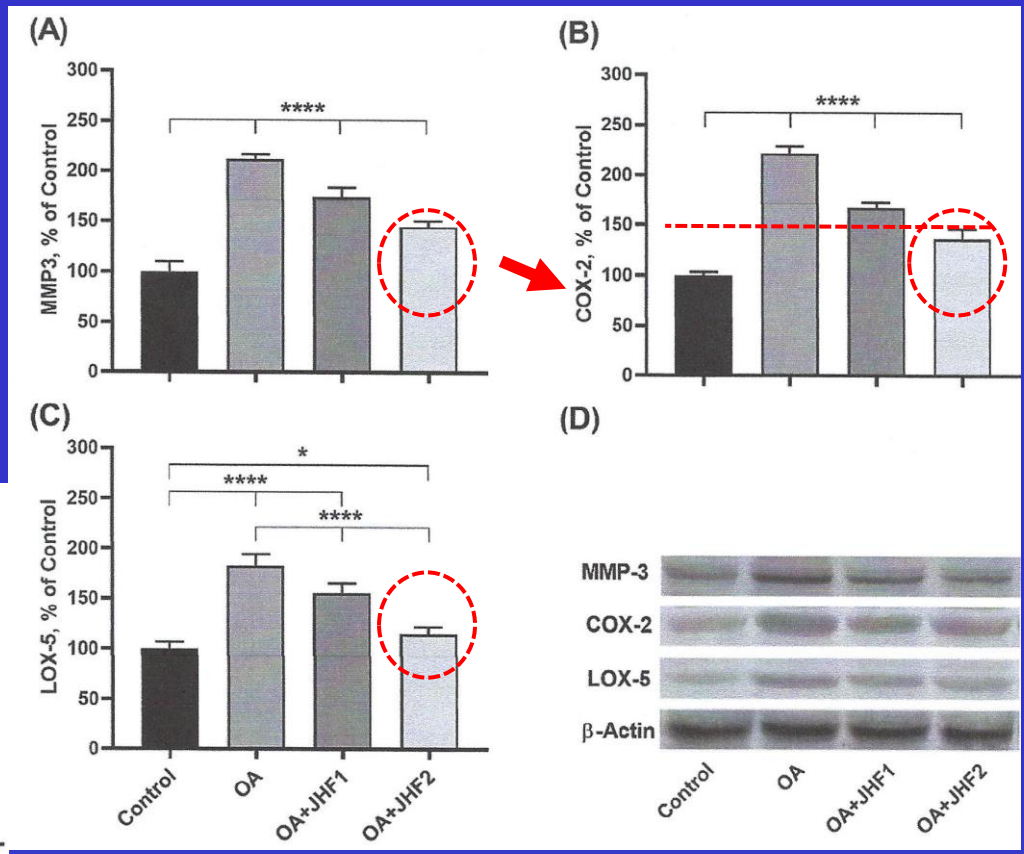
Phytochemicals Enhancing Insulin

Akdad et al. ANTIDIABETIC PHYTOCOMPOUNDS ACTING AS GLUCOSE TRANSPORT STIMULATORS. Endocr Metab Immune Disord Drug Targets, 2022 May 10. Online ahead of print.

The Impact Curcumin & Boswellia on OA

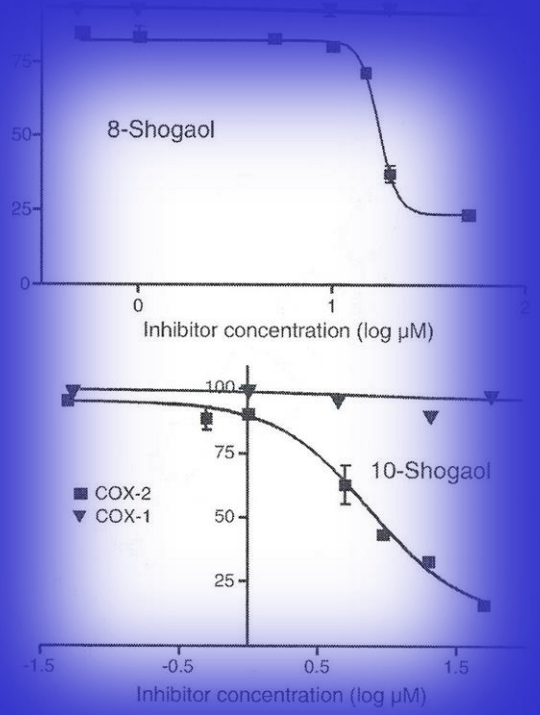






Orhan et al. PROTECTIVE EFFECT OF A NOVEL POLYHERBAL FORMULATION ON EXPERIMENTALLY INDUCED OSTEOARTHRITIS IN A RAT MODEL. Biomedicine & Pharmacotherapy, 2022;151:113052.

Inherent Safety of Herbal Polyphenols in Inflammatory Inhibition



They weakly inhibit NκFB and therefore allow sufficient COX enzyme activity for SPM production.

They are highly selective to inducible COX-2, sparing constitutive COX-1.

Van Breemen et al. CYCLOOXYGENASE-2 INHIBITORS IN GINGER. Fitoterapia, 2011; 82:38-43.

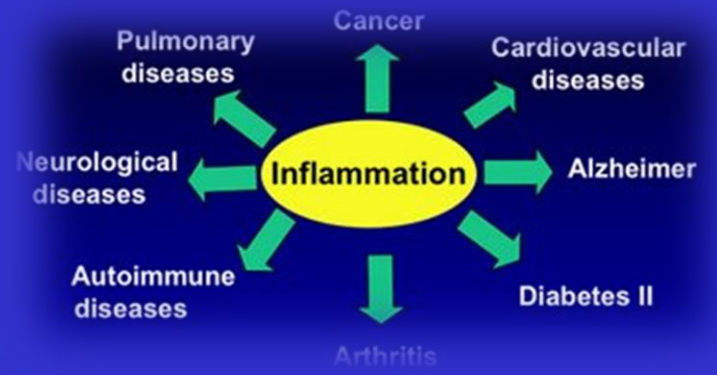
Polyphenolic Research/Literature

Polyphenolic	"Inflammation"		Total	
Curcumin	494	*2497*	5222	19,021
Resveratrol	386	*2026*	4930	15,572
Green Tea	238		4732	
Berberine				
Ginger	74	4783	1568	400
Silymarin	71		1753	
Grape Seed	60		1129	
Boswellia Serrata	28	136	258	832
Rosemary	22		233	
Quercetin		1822		23,195

PubMed – August, 2012

- April, 2022

The Essence if Chronic Inflammation

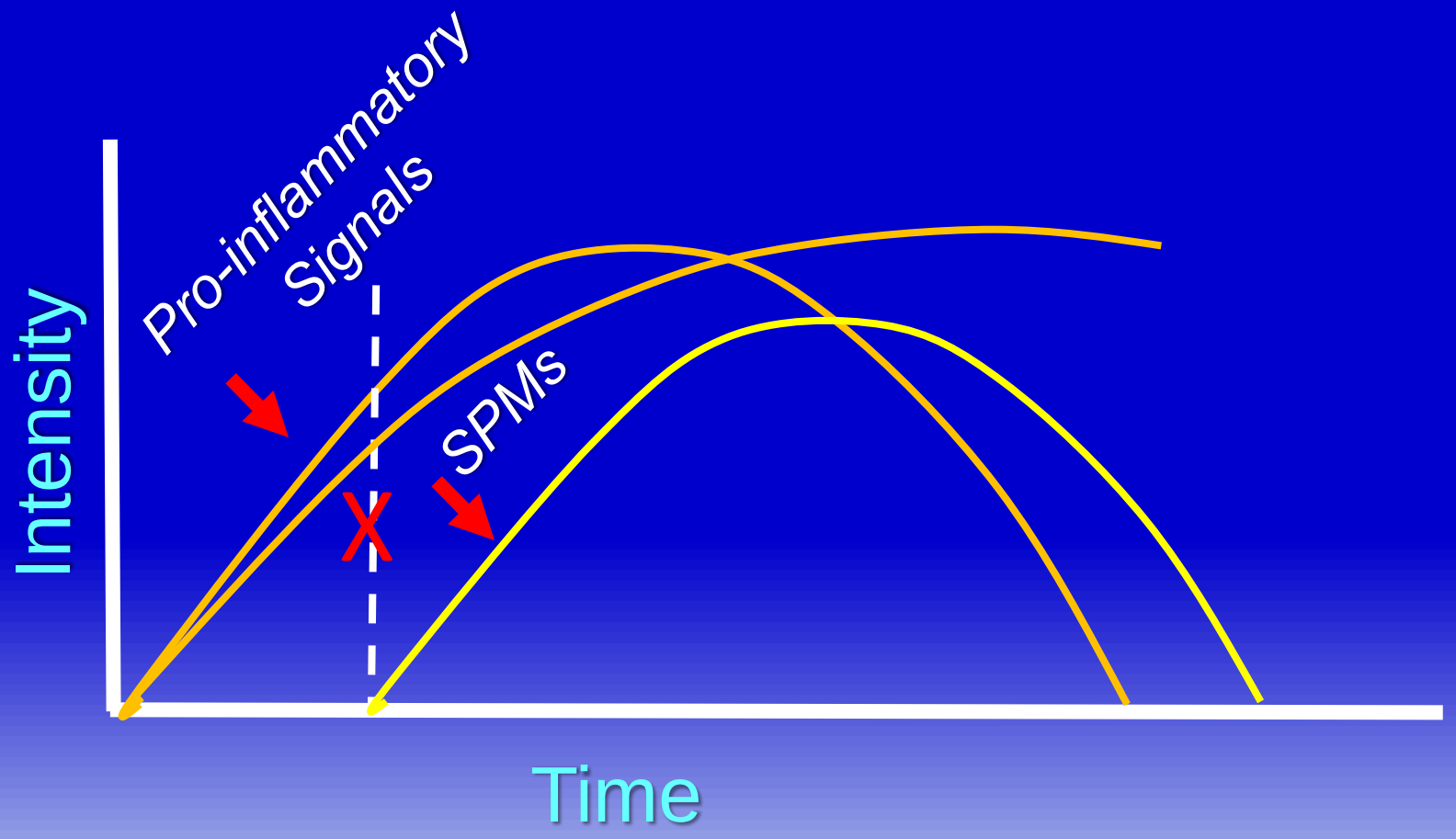


"Perhaps no single phenomenon contributes more to medical burden in industrialized societies than non-resolving inflammation."

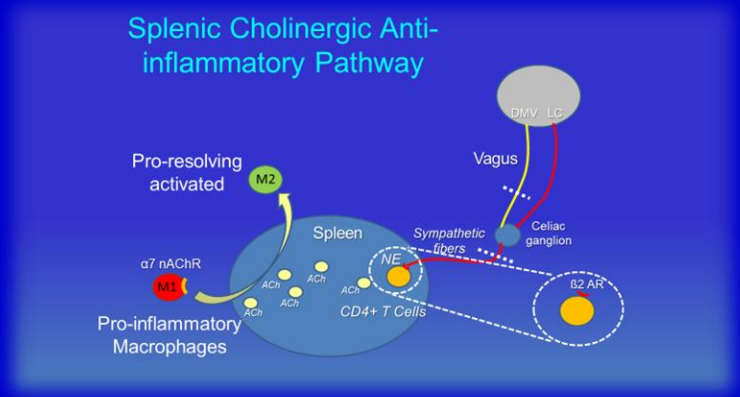
"The problem with inflammation is not how often it starts, but how often it fails to subside."

Nathan C, Ding A. NONRESOLVING INFLAMMATION. Cell, 2010;140:871-882.

Inflammatory/Anti-inflammatory Coordination



Vagal stimulation

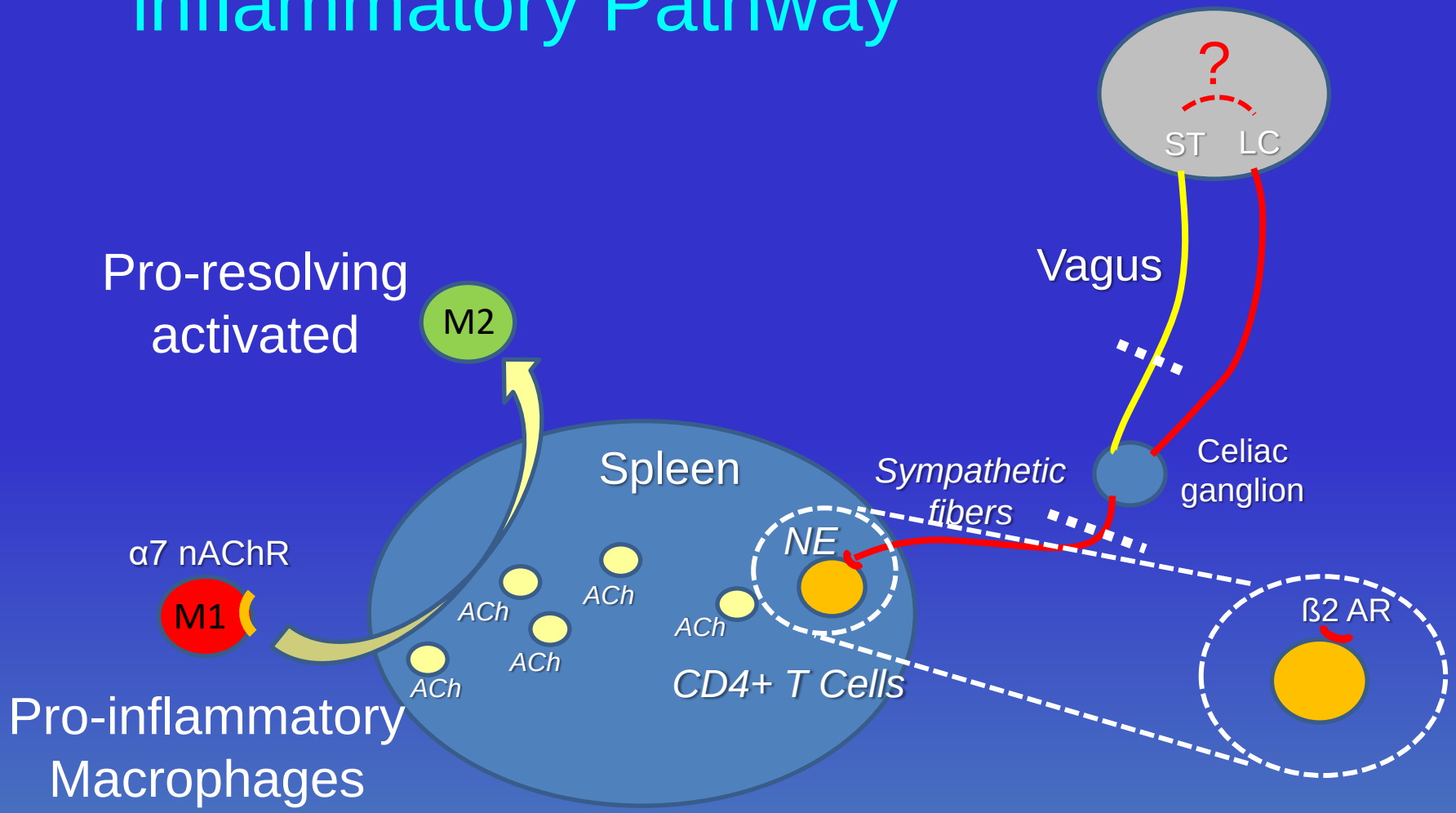


The transition from the inflammatory to anti-inflammatory/pro-resolving state is mediated by the vagus nerve.

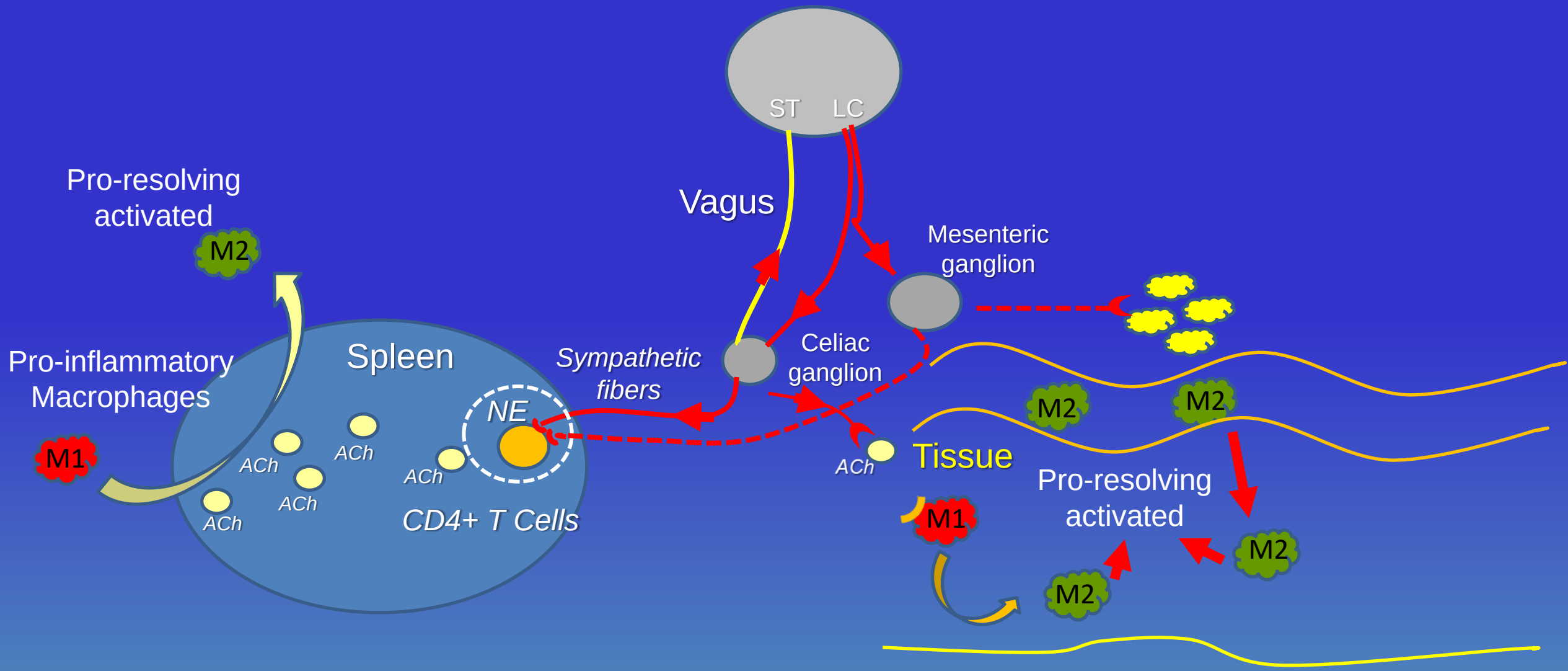
Inflammation does not “burn itself out” but it rather is suppressed by production of specialized pro-resolving mediators or SPMs from cell membrane omega-3 FAs.

Stimulation of the vagus nerve elicits the splenic cholinergic anti-inflammatory pathway.

Splenic Cholinergic Anti-inflammatory Pathway



Splenic Cholinergic Anti-inflammatory Pathway



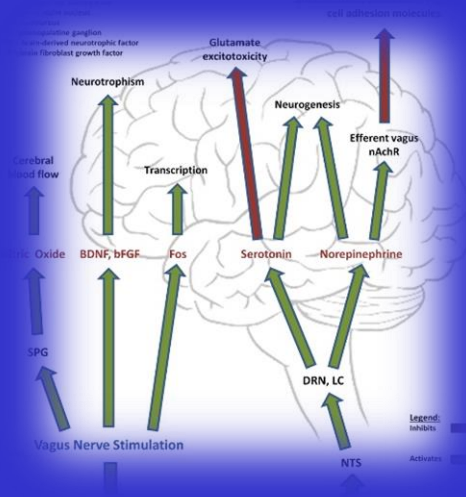
Vagus Nerve Stimulation in Treatment Non-responsive RA

After 12 weeks, five of 10 patients in the stimulation groups had a clinically meaningful response, measured by changes in Disease Activity Score in 28 joints and C-reactive protein (DAS28-CRP). Two patients achieved DAS28-CRP remission, but there was an "overall lack of DAS response in the sham group," Genovese reported.

In the stimulation groups, there was also a drop of more than 30% in levels of interleukin (IL)-1-beta, IL-6, and TNF-alpha.

European League Against Rheumatism (EULAR) 2019 Congress: Abstract LB0009. Presented June 15, 2019.

Vagal Nerve Stimulation

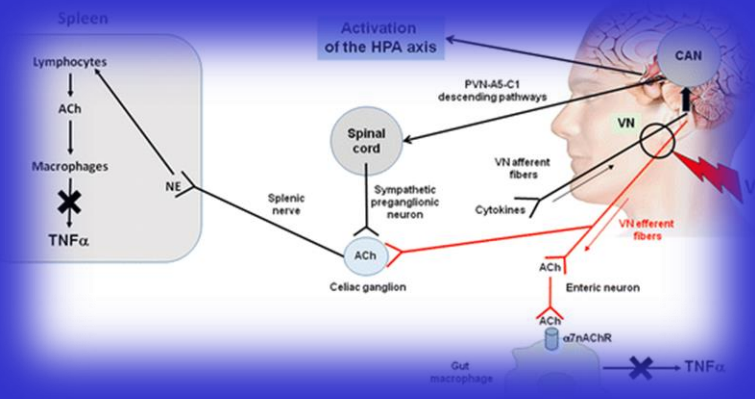


Rheumatoid arthritis
Inflammation
Primary headache
Gastric mucosal injury
IBD
Obesity
Hypertension
Diabetes

Epilepsy
GI motility disorders
Depression/anxiety
Stroke & TBI recovery
Cognitive function
Sleep
Atrial fibrillation
Heart failure
SVT in pregnancy

PubMed	*2015*	*2022*
VNS	8941	11,286
VNS/Inflam	292	585

Vagus Nerve Stimulation as Anti-inflammatory Therapy



"VNS interacts with the body's immune system to modify inflammatory tone by altering the release of pro- and anti-inflammatory cytokines."

"There is an ***overwhelming evidence*** to suggest that vagus nerve is an important component of the immune response and manipulating vagal tone is a way to modulate the immune system."

Johnson RL, Wilson CG. A REVIEW OF VAGUS NERVE STIMULATION AS A THERAPEUTIC INTERVENTION. Journal of Inflammation Research 2018:11 203–213.

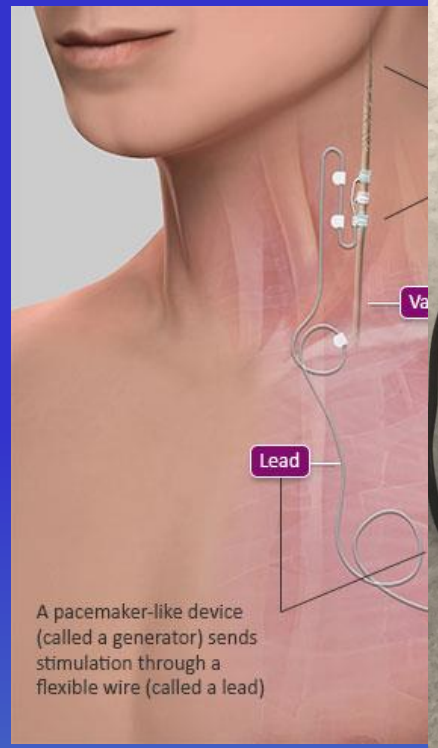
Emerging Research on tVNS

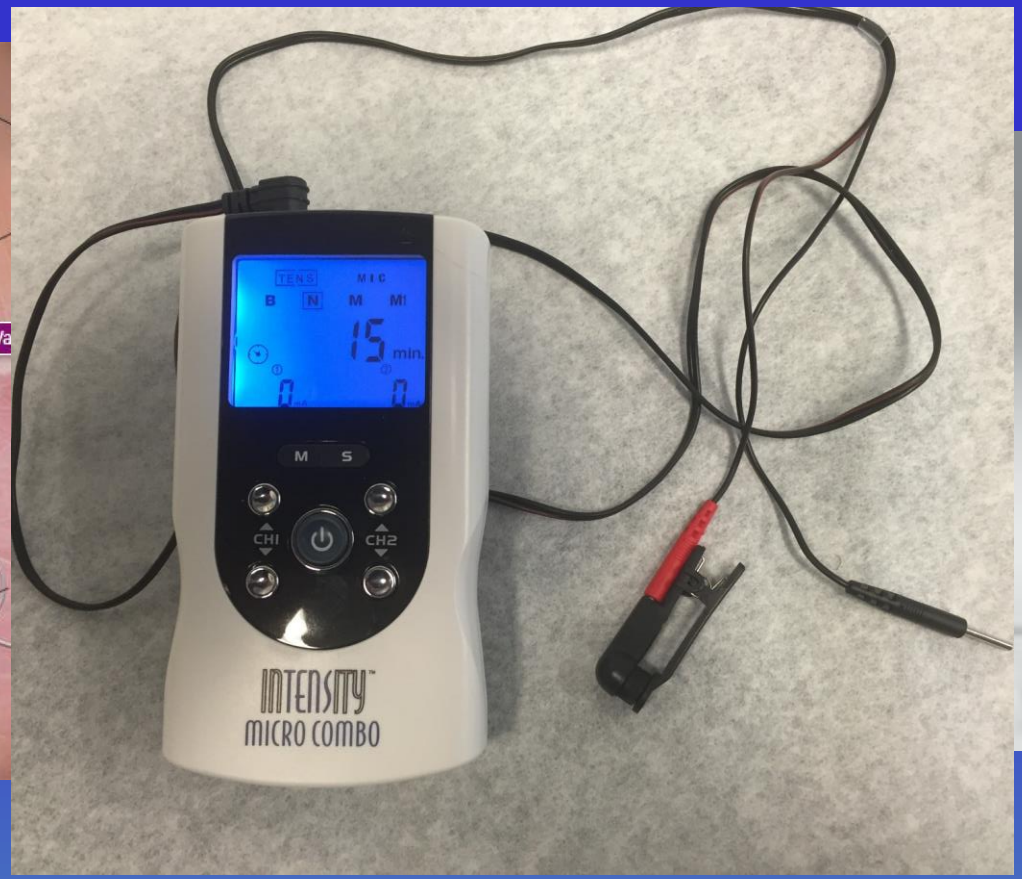
Vagal nerve stimulation additionally appears to act through celiac ganglion stimulation to have similar pro-resolving effects on resident macrophages in diverse group of innervated/tissue/organs.

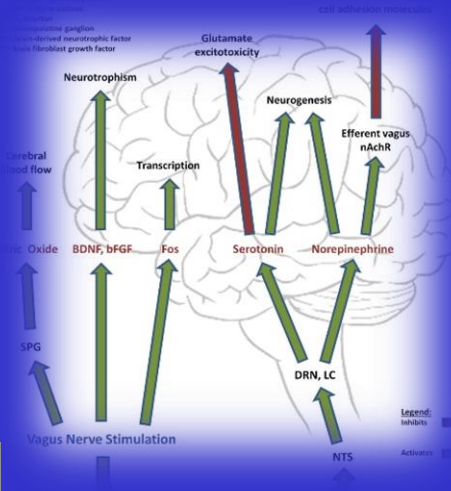
Phenols with pro-resolving effects appear to be positive allosteric modulator of a7-nACh receptor in diverse tissues.

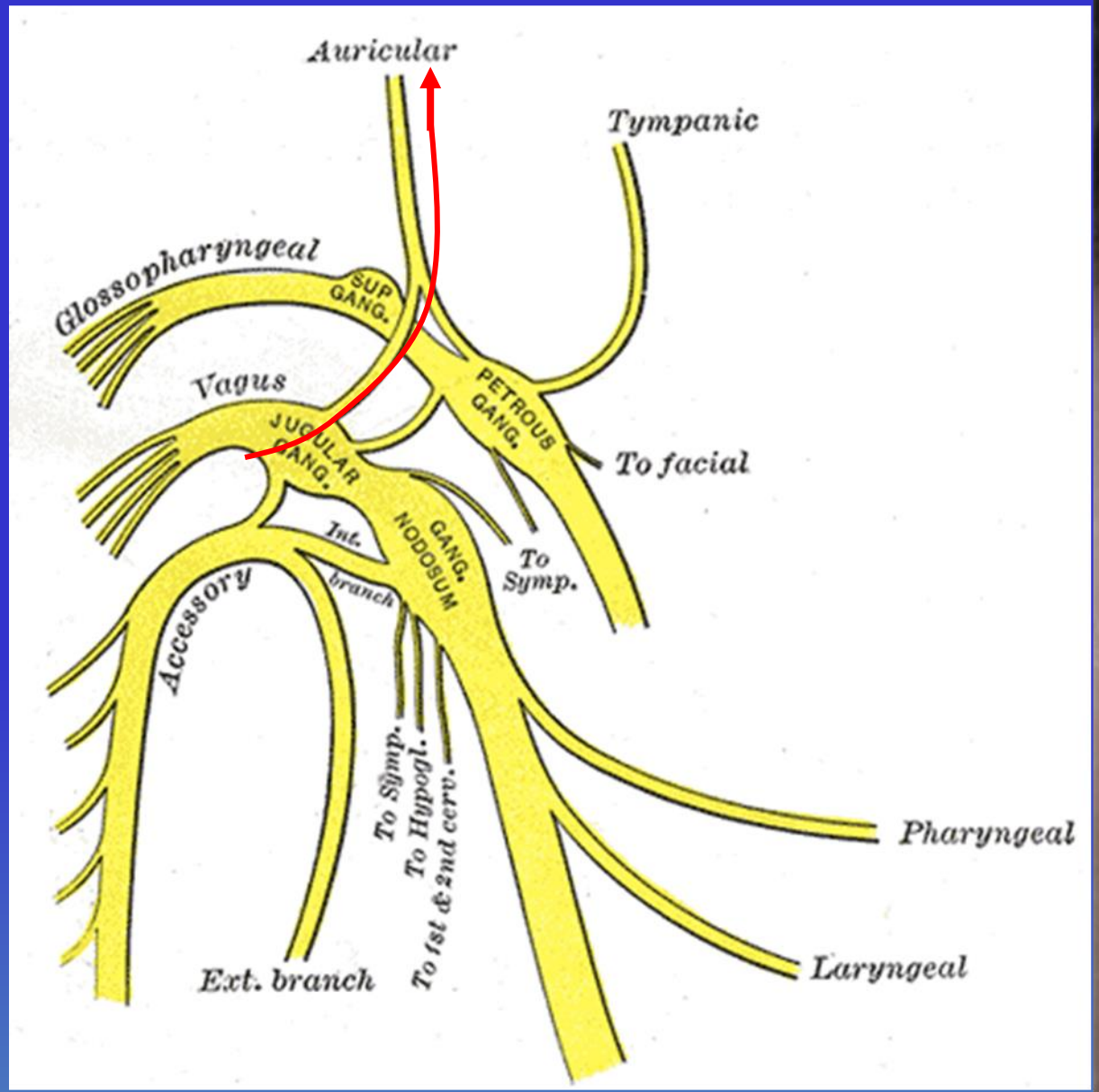
"Collectively, our results indicate that curcumin is a positive allosteric modulator of a7-nACh receptor and reverses nociception in mouse models of tonic and visceral pain."

El Nebrisi et al. CURCUMIN ACTS AS A POSITIVE ALLOSTERIC MODULATOR OF A7-NICOTINIC ACETYLCHOLINE RECEPTORS AND REVERSES NOCICEPTION IN MOUSE MODELS OF INFLAMMATORY PAINS. J Pharmacol Exp Ther, 2018;365:190–200.

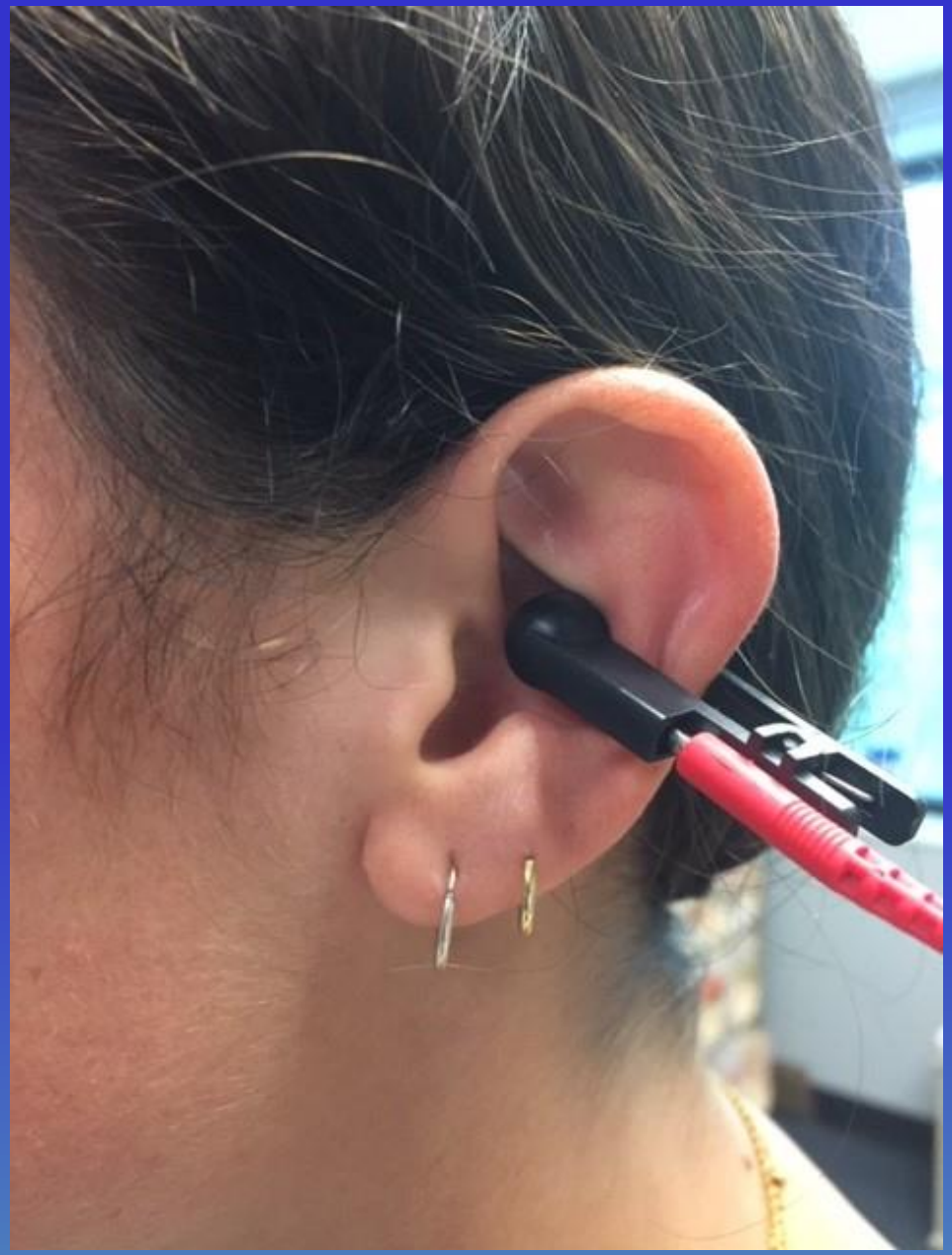

Lead
A pacemaker-like device (called a generator) sends stimulation through a flexible wire (called a lead)


TENS
M
S
CH1
CH2
INTENSITY
MICRO COMBO

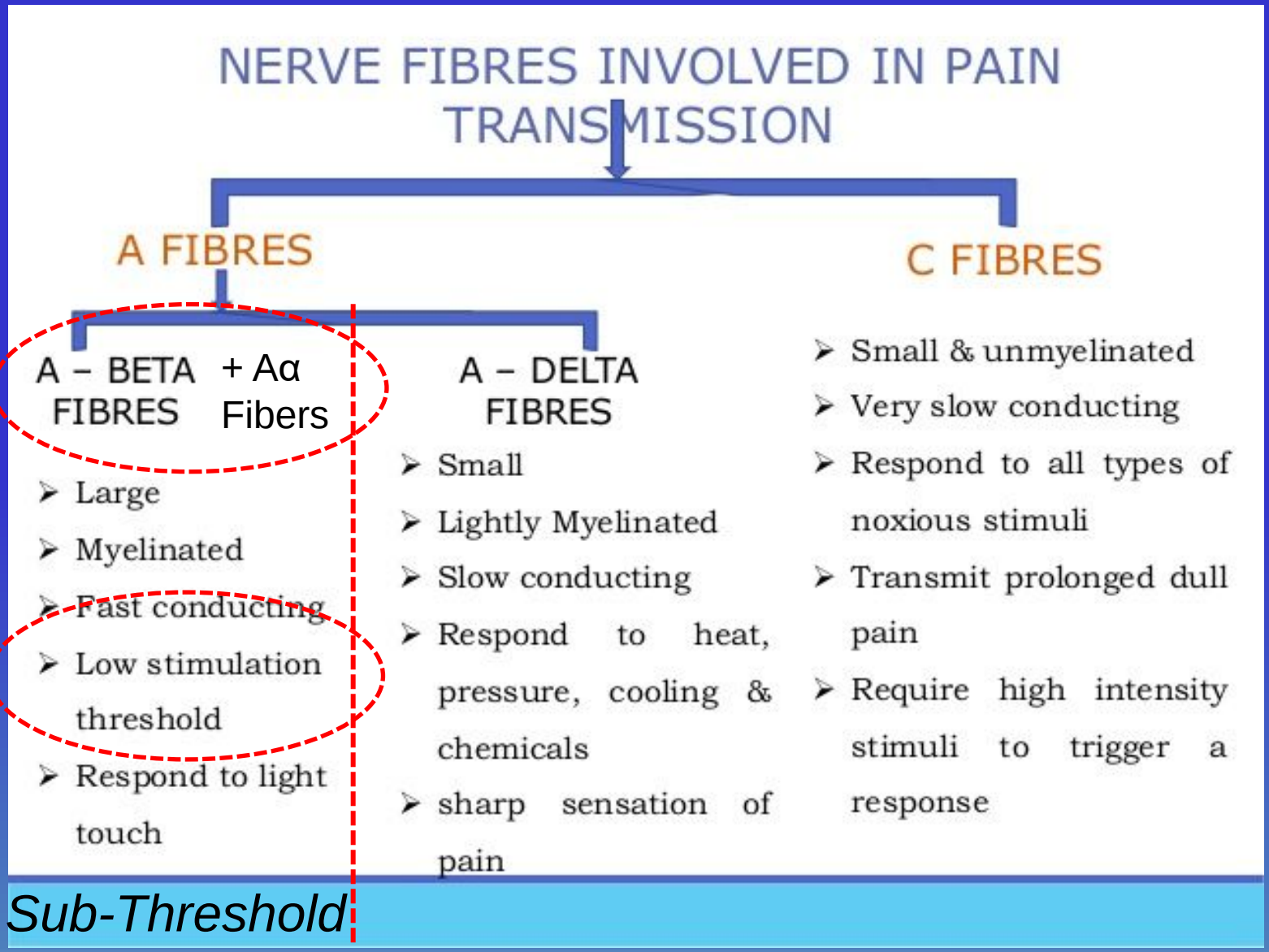

Glutamate excitotoxicity
Neurotrophism
Neurogenesis
Efferent vagus nAchR
Transcription
Oxide
BDNF, bFGF
Fos
Serotonin
Norepinephrine
SPG
DRN, LC
NTS
Vagus Nerve Stimulation


Auricular
Tympanic
Glossopharyngeal
SUP GANG.
Vagus
JUGULAR GANG.
PETROUS GANG.
To facial
Int. branch
GANG. NODOSUM
To Symp.
Accessory
To Symp.
To Hypogl.
To 1st & 2nd cerv.
Pharyngeal
Laryngeal
Ext. branch

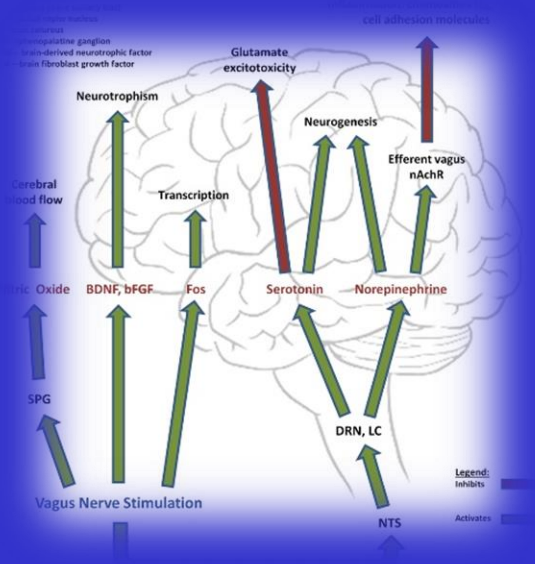

CyC
T
C



Critical Intensity Threshold for tVNS



tVNS Parameters



Stimulate the left tragus

Current parameters:

10-30 hz (vary weekly)
200 usec
1-2 mA – light perception
15 minutes

Contraindications

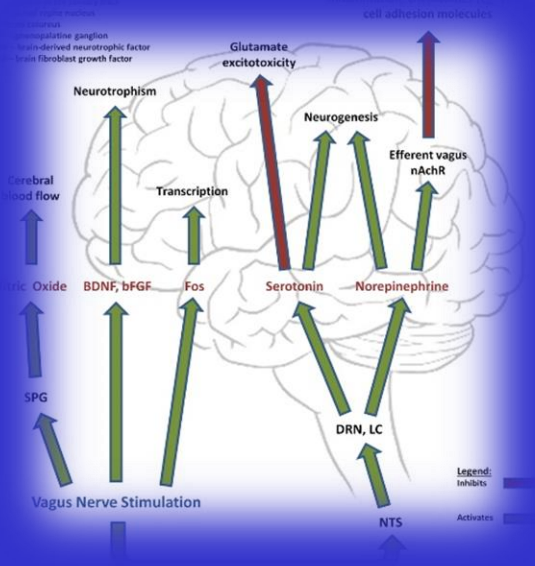
Implanted stimulators (cardiac, vagal);
~~atrial fibrillation~~;

Precautions

Asthma, COPD, Atrial fib, orthostatic intolerance

Bonaz B. PARAMETERS MATTER: MODULATING CYTOKINES USING NERVE STIMULATION. Bioelectronic Medicine, 2020;6, #12.

Safety and Tolerability of tVNS



tVNS has been safe and well tolerated by research participants to date.

The most common side effect of tVNS was skin irritation (in 18.2%).

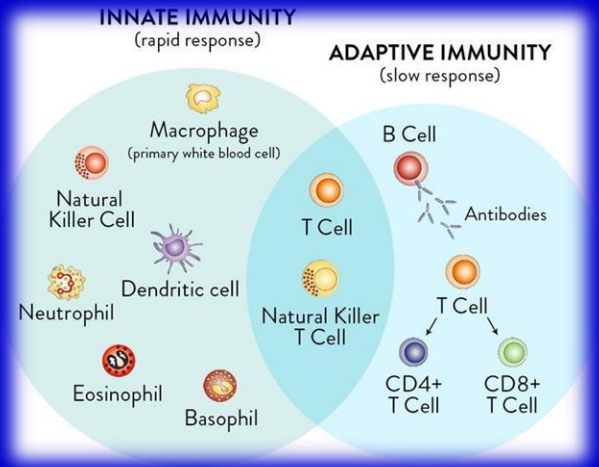
35 (2.6%) tVNS treated participants dropped out of studies due to side effects.

3 serious adverse events were “possibly” due to tVNS (out of 1322 participants treated).

Symptomatic bradycardia occurred in 1 (0.08%) subject.

Redgrave et al. SAFETY AND TOLERABILITY OF TRANSCUTANEOUS VAGUS NERVE STIMULATION IN HUMANS; A SYSTEMATIC REVIEW. Brain Stimulation, 2018;11:1225-1238.

Age Related Immune Functional Changes – Thymic Involution



The thymus gland reaches peak weigh at about 10 years.

It declines 3% yearly until the third decade. *- 60%*

Decline continues from the 3rd decade at 1% per year until death. *- 80% by age 50*

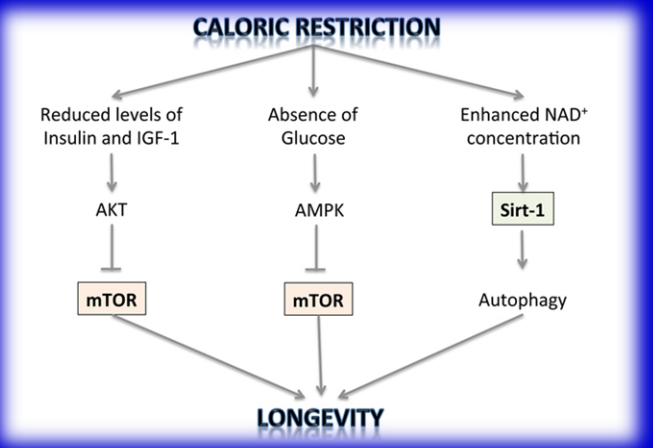
Thymus Involution

“Together, these findings demonstrate that age-related thymic involution is involved not only in immunosenescence associated with the insufficient output of naïve T cells, but also in the emergence of inflammaging via the increased release of autoreactive T cells.”

“Therefore, therapeutically targeting thymic involution should present a promising strategy for attenuating chronic inflammation, thereby reducing a major risk factor associated with morbidity and mortality in virtually every chronic age-related disease.”

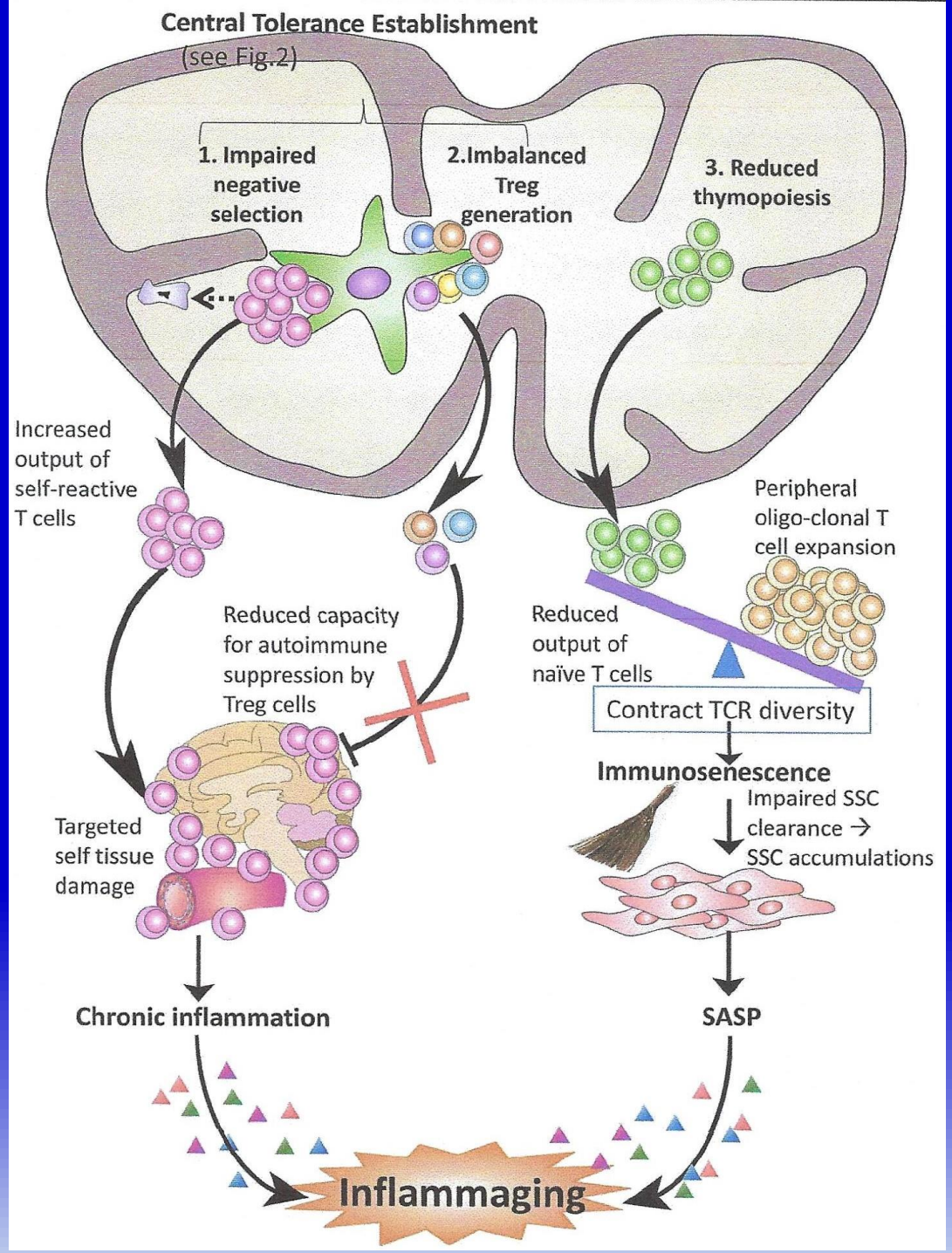
Coder B, Su D-M. THYMIC INVOLUTION BEYOND T-CELL INSUFFICIENCY. Oncotarget. 2015 Sep 8; 6(26): 21777–21778.

Caloric Restriction Thymus Glad Regeneration

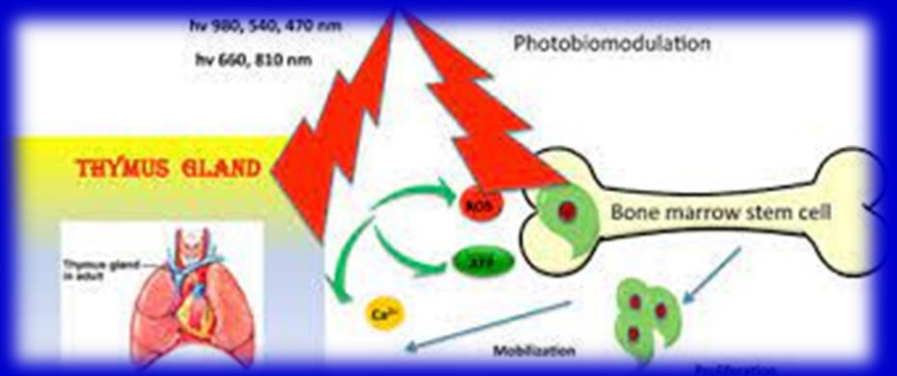


"We report that about 14% CR for 2 years in healthy humans improved thymopoiesis and was correlated with mobilization of intra-thymic ectopic lipid. CR-induced transcriptional reprogramming in adipose tissue implicated pathways regulating mitochondrial bioenergetics, anti-inflammatory responses, and longevity."

Sadaro et al. CALORIC RESTRICTION IN HUMANS REVEALS IMMUNOMETABOLIC REGULATORS OF HEALTH SPAN. SCIENCE, 2022;375:671-677.


Central Tolerance Establishment
(see Fig.2)
1. Impaired negative selection
2.Imbalanced Treg generation
3. Reduced thymopoiesis
Increased output of self-reactive T cells
Reduced capacity for autoimmune suppression by Treg cells
Targeted self tissue damage
Chronic inflammation
Peripheral oligo-clonal T cell expansion
Reduced output of naïve T cells
Contract TCR diversity
Immunosenescence
Impaired SSC clearance → SSC accumulations
SASP
Inflammaging

Increasing Alpha-1-thymosin



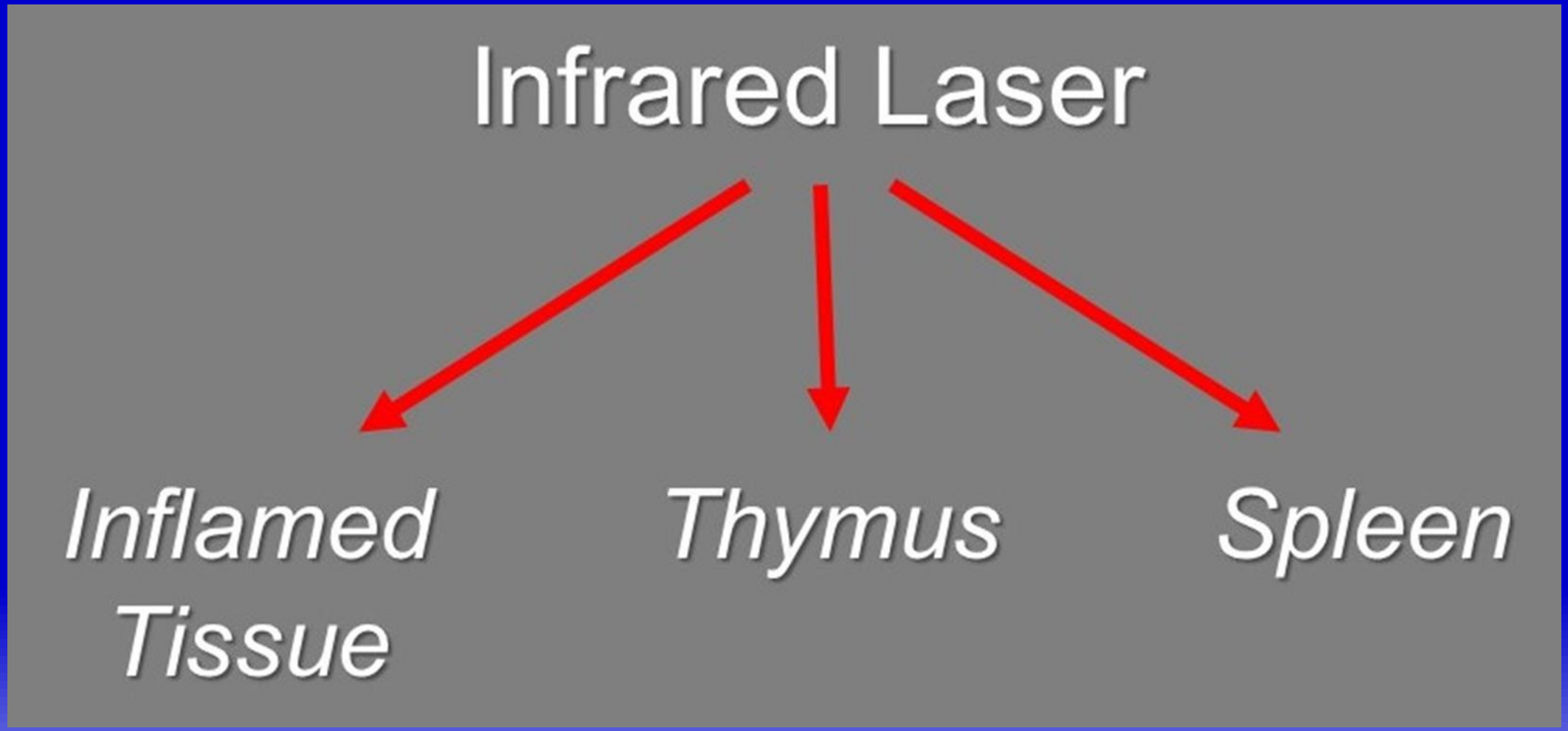
Local irradiation with pulsed (1500 Hz) low-energy infrared laser light of the thymus and thyroid gland region caused well-apparent stimulation of alpha-1-thymosin production in the healthy animals and normalized its level in the stressed ones. Similar stimulation of alpha-1-thymosin biosynthesis was observed in an experiment with direct laser irradiation of the cultured HTSC epitheliocytes from the human thymus.

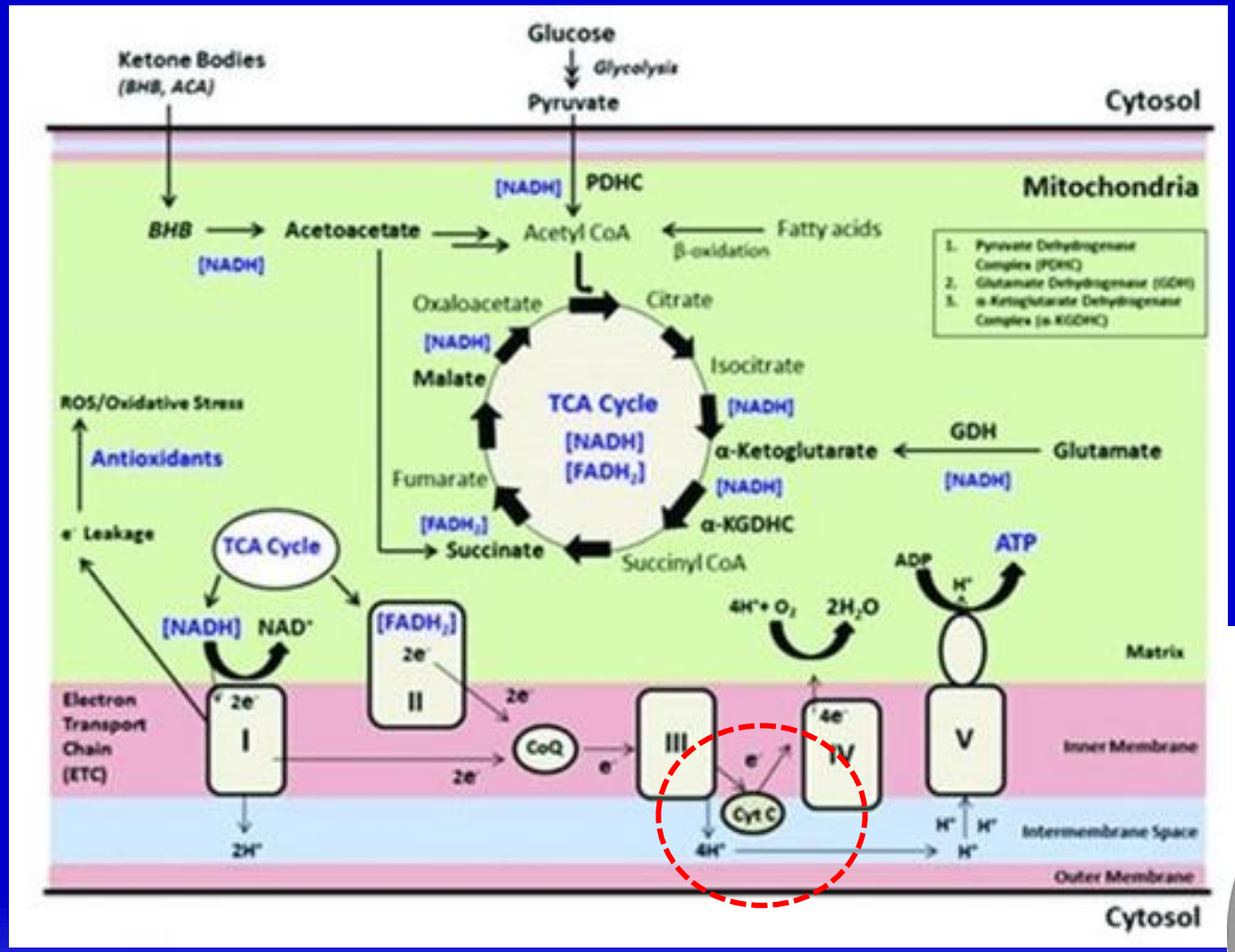
Pershin et al. THE INFLUENCE OF PULSED INFRARED LASER RADIATION ON THE HORMONE PRODUCTION IN THE THYMUS (AN EXPERIMENTAL STUDY. Vopr Kurortol Fizioter Lech Fiz Kult, Jul-Aug 2011;(4):39-42.

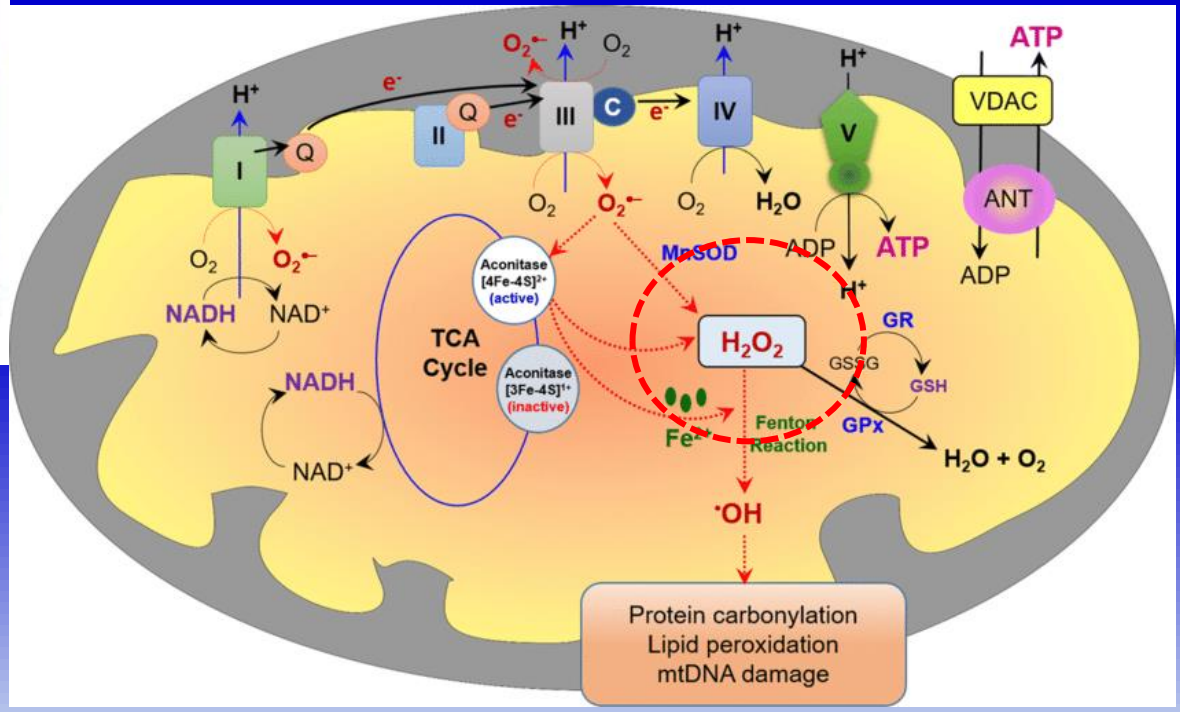
Photobiomodulation and Inflammatory Regulation

“Our results reveal that red/NIR light does not change the cytokine profile in non-activated macrophages. To the contrary, in activated macrophages, light inhibits the production of pro-inflammatory cytokines (TNF-α, IL-1 and IL-6) up to two times and activates the secretion of anti-inflammatory cytokines (IL-10 and TGF-β) by several times.”

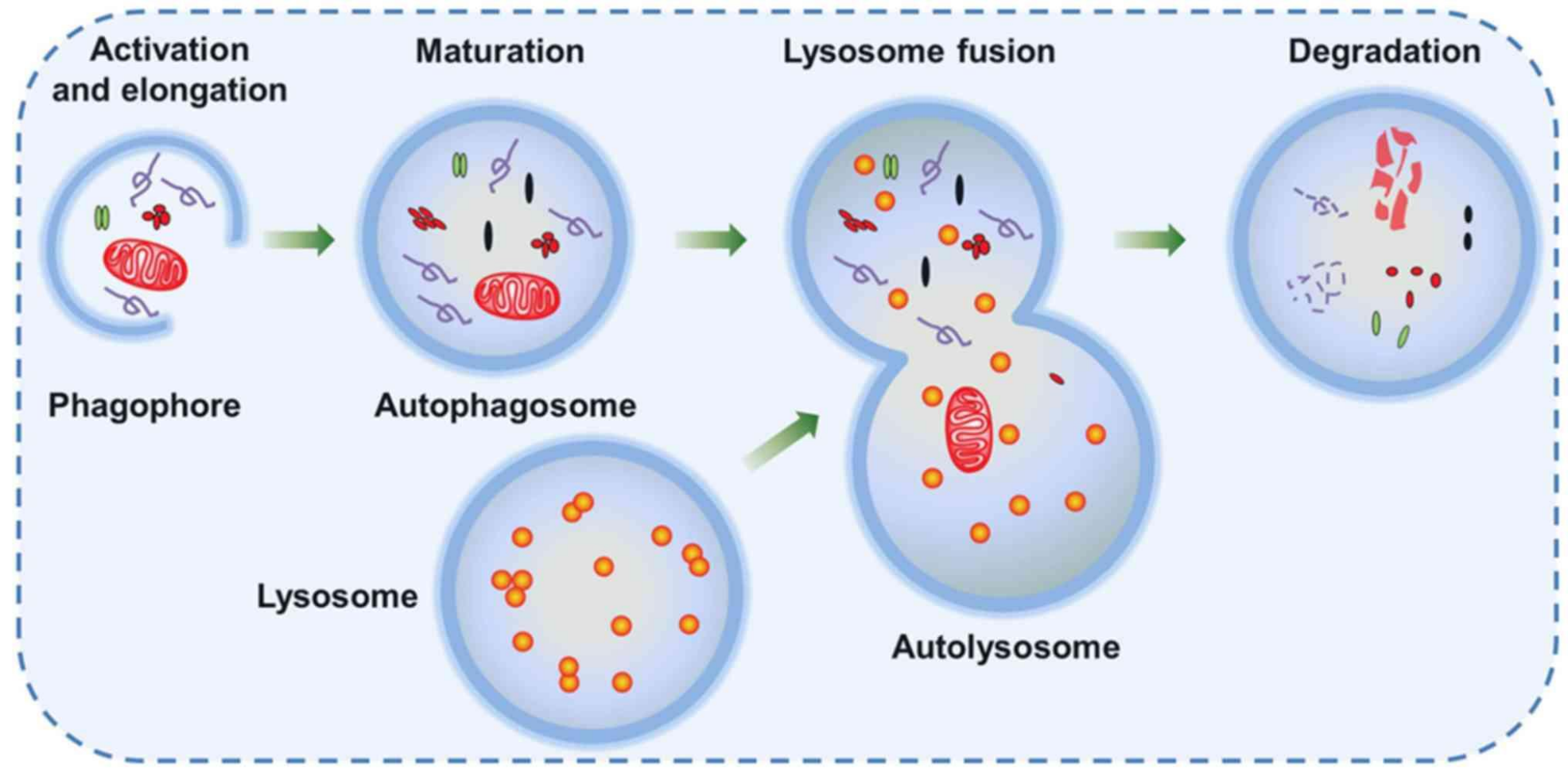
Golovynska et al. MACROPHAGES MODULATED BY RED/NIR LIGHT: PHAGOCYTOSIS, CYTOKINES, MITOCHONDRIAL ACTIVITY, CA2+ INFLUX, MEMBRANE DEPOLARIZATION AND VIABILITY. Photochemistry and Photobiology, 27 September 2021.

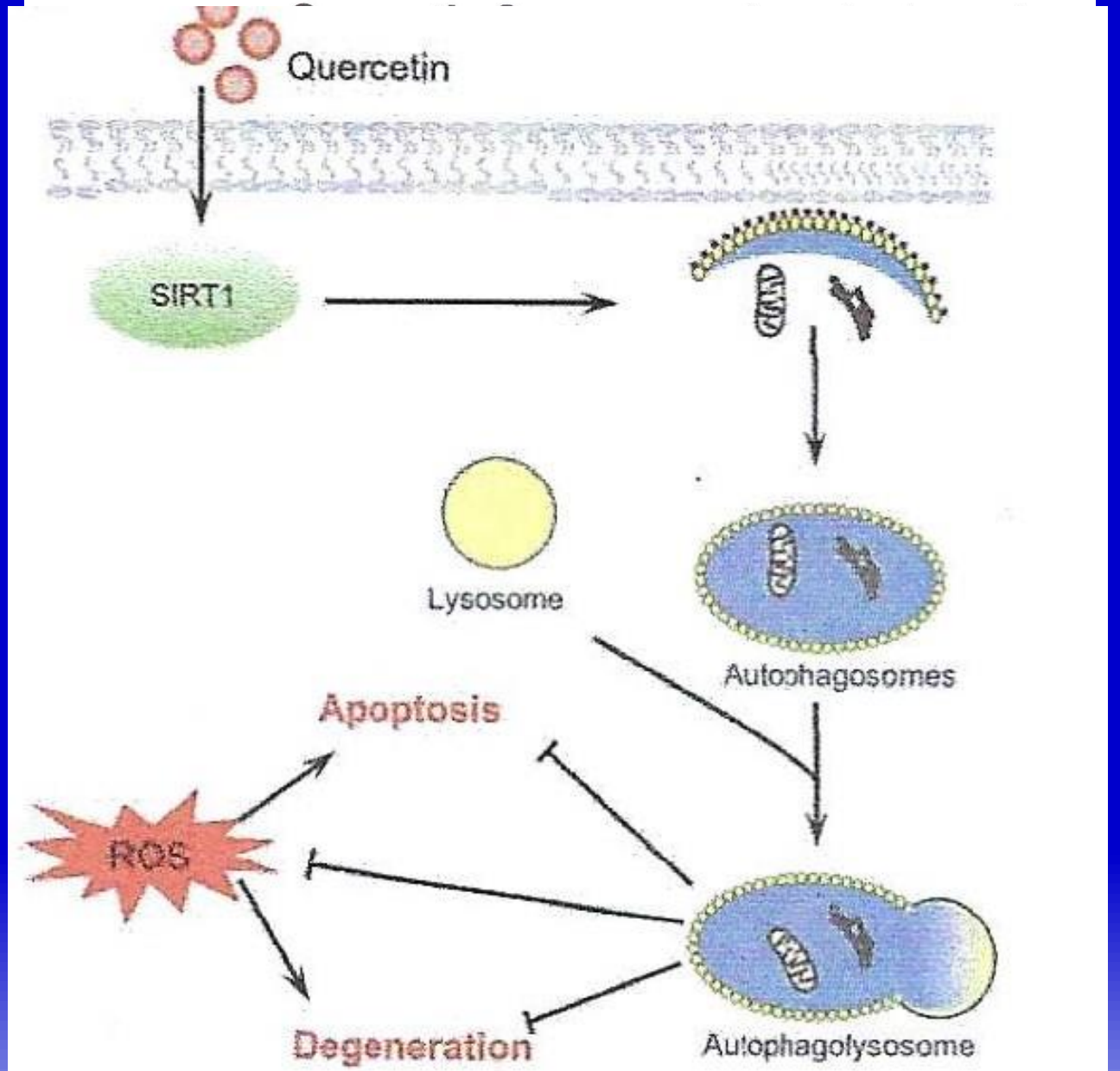

Infrared Laser
Inflamed Tissue
Thymus
Spleen


Ketone Bodies
(BHB, ACA)
Glucose
Glycolysis
Pyruvate
Cytosol
[NADH]
PDHC
Mitochondria
BHB
Acetoacetate
[NADH]
Acetyl CoA
Fatty acids
β-oxidation
1. Pyruvate Dehydrogenase Complex (PDHC)
2. Glutamate Dehydrogenase (GDH)
3. α-Ketoglutarate Dehydrogenase Complex (α-KGDHC)
Oxaloacetate
[NADH]
Malate
Citrate
Isocitrate
[NADH]
TCA Cycle
[NADH]
[FADH2]
α-Ketoglutarate
GDH
Glutamate
[NADH]
[NADH]
α-KGDHC
Fumarate
[FADH2]
Succinate
Succinyl CoA
ROS/Oxidative Stress
Antioxidants
e⁻ Leakage
TCA Cycle
[NADH] NAD+
[FADH2]
2e⁻
ADP
ATP
H+
4H+ + O2
2H2O
Matrix
Electron Transport Chain (ETC)
I
II
III
IV
V
CoQ
Cyt C
4e⁻
2e⁻
e⁻
2H+
4H+
Inner Membrane
Intermembrane Space
Outer Membrane
Cytosol


ATP
VDAC
ANT
ADP
H+
O2
O2•−
e⁻
I
II
III
IV
V
Q
C
H2O
NADH
NAD+
TCA Cycle
Aconitase [4Fe-4S]2+ (active)
Aconitase [3Fe-4S]1+ (inactive)
MnSOD
H2O2
GR
GSSG
GSH
GPx
Fenton Reaction
Fe2+
•OH
H2O + O2
Protein carbonylation
Lipid peroxidation
mtDNA damage

Autophagy


Activation
and elongation
Maturation
Lysosome fusion
Degradation
Phagophore
Autophagosome
Lysosome
Autolysosome


Quercetin
SIRT1
Lysosome
Autophagosomes
Apoptosis
ROS
Degeneration
Autophagolysosome

Inflammation, such a problem…

… but so many solutions!

For Monday…

- Look and talk about diet
- Have resolution supplies in the warehouse
- Add phenolics from herbs
- Use vagal nerve stimulation
- Broadly target with laser
- Stimulate autophagy