Immuno-Musculoskeletal Nutrition

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Affiliations

ANABOLIC LABORATORIES

NCMIC
We Take Care of Our Own

DeFlame
No Nonsense Nutrition
For Inflammation Reduction

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Example of symptoms caused by hypocapnia = respiratory alkalosis:

- apprehension
- faintness
- fatigue
- headache
- impaired concentration
- giddiness
- irritability
- seizure
- weakness
- visual disturbances
- diaphoresis
- perioral numbness
- dyspnea
- palpations
- tachycardia
- abdominal discomfort
- chest pain
- air swallowing
- breathlessness
- yawning and/or sighing
- dry mouth
- tetany
- muscle tightening & stiffness
- distal paresthesias

1. Duncan S, Raffin T. Handling hyperventilation syndrome. Hosp Med. 1992;28:58-67.
2. Rice RL. Symptom patterns of the hyperventilation syndrome. Am J Med. 1950;8:691-700.

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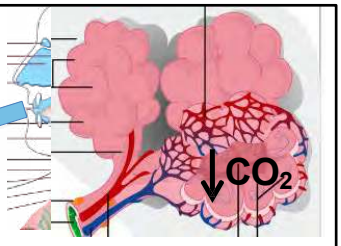
Problem in a nutshell



$\uparrow CO_2$

Henderson-Hasselbalch equation = pH regulation of extracellular fluids

$$pH = \frac{HCO_3^-}{CO_2} = \text{Alkaline pH}$$

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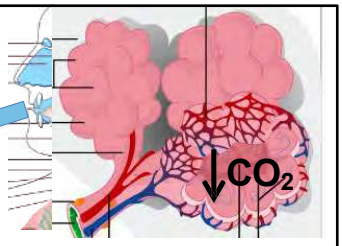
Problem in a nutshell



↑CO_2

At the end of exhalation, the amount of CO_2 in the alveoli is allocated to the alveolar capillaries, which means that end tidal CO_2 ($ETCO_2$) = arterial CO_2 ($PaCO_2$).

$ETCO_2$ below 35 mm HG = systemic alkalosis, vasoconstriction, increased sodium conductance, and debilitating symptoms.

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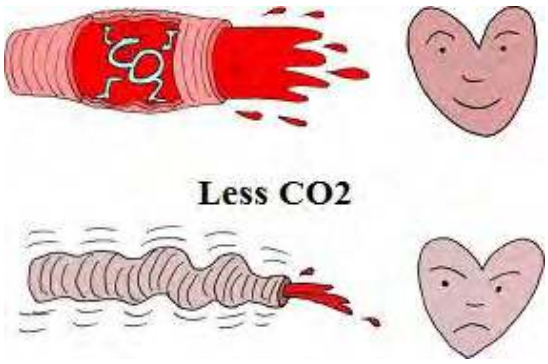
Low CO2 = alkalosis = vasoconstriction



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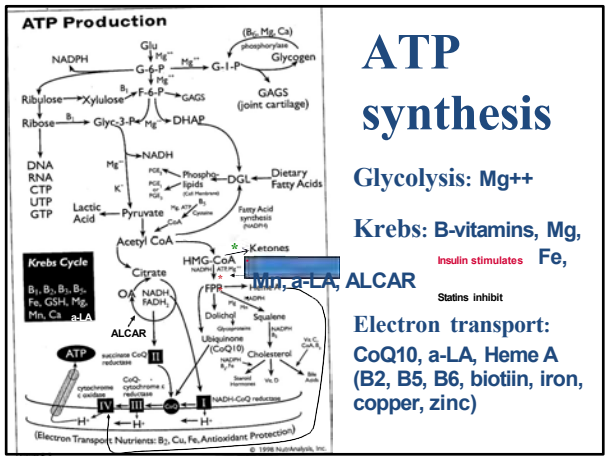

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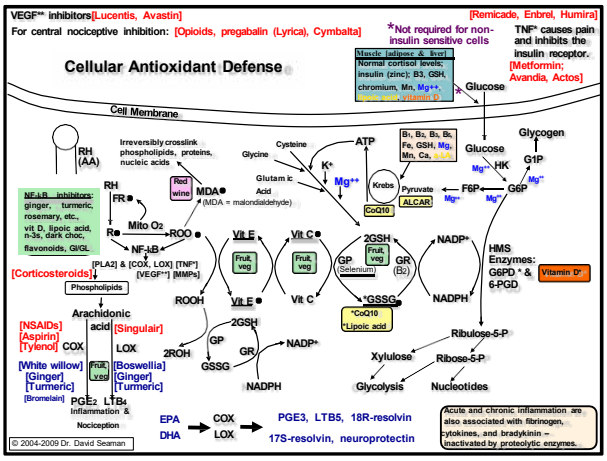

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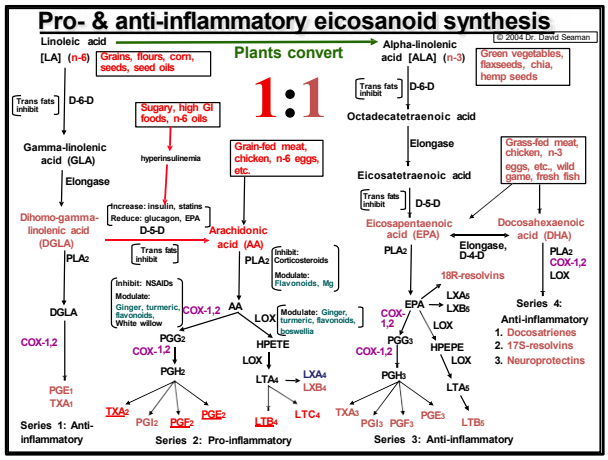

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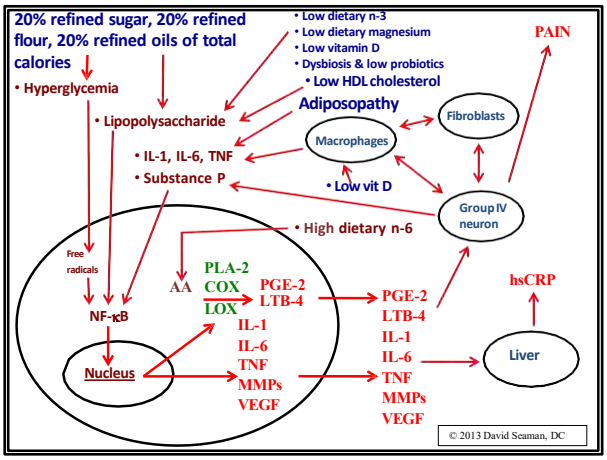

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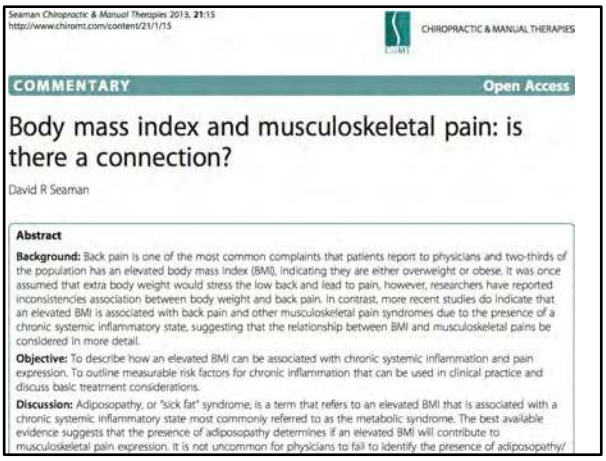

Seaman *Chiropractic & Manual Therapies* 2013, **21**:15
http://www.chiromt.com/content/21/1/15

CHIROPRACTIC & MANUAL THERAPIES

COMMENTARY Open Access

Body mass index and musculoskeletal pain: is there a connection?

David R Seaman

Abstract

Background: Back pain is one of the most common complaints that patients report to physicians and two-thirds of the population has an elevated body mass index (BMI), indicating they are either overweight or obese. It was once assumed that extra body weight would stress the low back and lead to pain, however, researchers have reported inconsistencies association between body weight and back pain. In contrast, more recent studies do indicate that an elevated BMI is associated with back pain and other musculoskeletal pain syndromes due to the presence of a chronic systemic inflammatory state, suggesting that the relationship between BMI and musculoskeletal pains be considered in more detail.

Objective: To describe how an elevated BMI can be associated with chronic systemic inflammation and pain expression. To outline measurable risk factors for chronic inflammation that can be used in clinical practice and discuss basic treatment considerations.

Discussion: Adiposopathy, or "sick fat" syndrome, is a term that refers to an elevated BMI that is associated with a chronic systemic inflammatory state most commonly referred to as the metabolic syndrome. The best available evidence suggests that the presence of adiposopathy determines if an elevated BMI will contribute to musculoskeletal pain expression. It is not uncommon for physicians to fail to identify the presence of adiposopathy/

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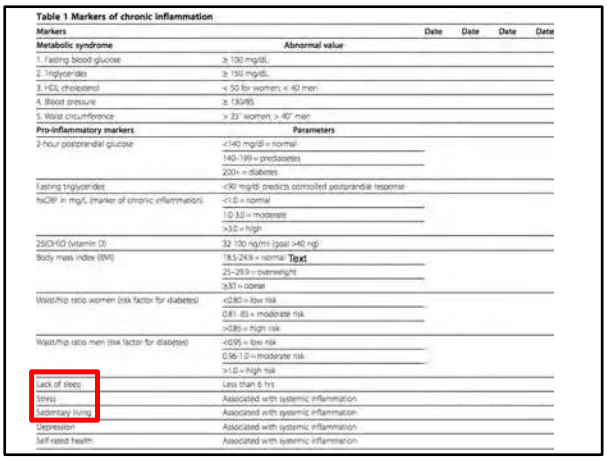

Table 1 Markers of chronic inflammation

Markers		Date	Date	Date	Date
Metabolic syndrome	**Abnormal value**				
1. Fasting blood glucose	≥ 100 mg/dL				
2. Triglycerides	≥ 150 mg/dL				
3. HDL cholesterol	< 50 for women; < 40 men				
4. Blood pressure	≥ 130/85				
5. Waist circumference	> 35" women; > 40" men				
Pro-inflammatory markers	**Parameters**				
2-hour postprandial glucose	<140 mg/dl = normal				
	140–199 = prediabetes				
	200+ = diabetes				
Fasting triglycerides	<90 mg/dl predicts controlled postprandial response				
hsCRP in mg/L (marker of chronic inflammation)	<1.0 = normal				
	1.0-3.0 = moderate				
	>3.0 = high				
25(OH)D (vitamin D)	32-100 ng/ml (goal >40 ng)				
Body mass index (BMI)	18.5-24.9 = normal **Text**				
	25–29.9 = overweight				
	≥30 = obese				
Waist/hip ratio women (risk factor for diabetes)	<0.80 = low risk				
	0.81–85 = moderate risk				
	>0.85 = high risk				
Waist/hip ratio men (risk factor for diabetes)	<0.95 = low risk				
	0.96-1.0 = moderate risk				
	>1.0 = high risk				
Lack of sleep	Less than 6 hrs				
Stress	Associated with systemic inflammation				
Sedentary living	Associated with systemic inflammation				
Depression	Associated with systemic inflammation				
Self-rated health	Associated with systemic inflammation				

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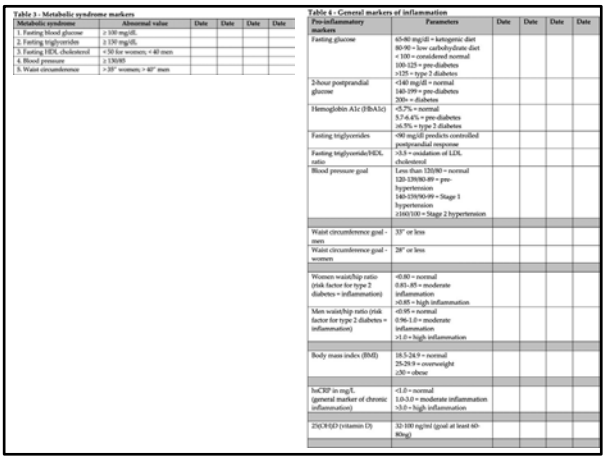

Table 3 - Metabolic syndrome markers

Metabolic syndrome	Abnormal value	Date	Date	Date	Date
1. Fasting blood glucose	≥ 100 mg/dL				
2. Fasting triglycerides	≥ 150 mg/dL				
3. Fasting HDL cholesterol	< 50 for women; < 40 men				
4. Blood pressure	≥ 130/85				
5. Waist circumference	> 35" women; > 40" men				

Table 4 - General markers of inflammation

Pro-inflammatory markers	Parameters	Date	Date	Date	Date
Fasting glucose	65-80 mg/dl = ketogenic diet 80-90 = low carbohydrate diet < 100 = considered normal 100-125 = pre-diabetes >125 = type 2 diabetes				
2-hour postprandial glucose	<140 mg/dl = normal 140-199 = pre-diabetes 200+ = diabetes				
Hemoglobin A1c (HbA1c)	<5.7% = normal 5.7-6.4% = pre-diabetes ≥6.5% = type 2 diabetes				
Fasting triglycerides	<90 mg/dl predicts controlled postprandial response				
Fasting triglyceride/HDL ratio	>3.8 = oxidation of LDL cholesterol				
Blood pressure goal	Less than 120/80 = normal 120-139/80-89 = pre-hypertension 140-159/90-99 = Stage 1 hypertension ≥160/100 = Stage 2 hypertension				
Waist circumference goal - men	35" or less				
Waist circumference goal - women	28" or less				
Women waist/hip ratio (risk factor for type 2 diabetes + inflammation)	<0.80 = normal 0.81-.85 = moderate inflammation >0.85 = high inflammation				
Men waist/hip ratio (risk factor for type 2 diabetes + inflammation)	<0.95 = normal 0.96-1.0 = moderate inflammation >1.0 = high inflammation				
Body mass index (BMI)	18.5-24.9 = normal 25-29.9 = overweight ≥30 = obese				
hsCRP in mg/L (general marker of chronic inflammation)	<1.0 = normal 1.0-3.0 = moderate inflammation >3.0 = high inflammation				
25(OH)D (vitamin D)	32-100 ng/ml (goal at least 60-80ng)				

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The DeFlame Diet approach

1. Avoid excess calories…weigh what you weighed when you were in high-school or college and maintain normal levels of inflammatory markers

2. Avoid empty calories (refined sugar, flour, and oils) and excess salt

3. Maximize your nutrient/calorie ratio (example of whole grains vs vegetables)

4. Dietary options:

Vegan

Omnivore

Carnivore

5. Supplements:

- **Multivitamin/mineral**
- **Magnesium (mag)**
- **Vitamin D (D)**
- **Omega-3 (3)**
- **Probiotics**
- **Polyphenols (ginger/turmeric, etc.)**
- **Iodine (contraindicated in Hashimoto's disease)**
- **Vitamin C**
- **Zinc**
- **CoQ10**
- **Glucosamine/chondroitin**

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Before DeFlaming

Before the eczema emerged, she suffered for years with cold sores, an itchy scalp and chronic musculoskeletal pain.

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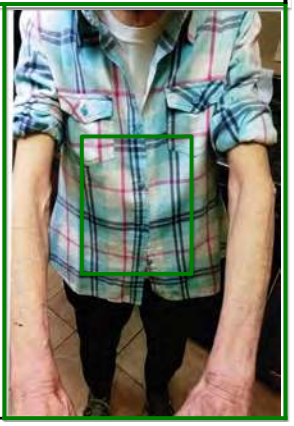
Before DeFlaming

After DeFlaming



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Modern diet - source of calories

10% dairy products

1-2% alcohol

20% refined grains/pasta/bread/cereal

20% refined sugars

20% refined vegetable/seed oils

15-20% obese meat

<10% vegetables, fruit (potatoes, legumes, whole grains)

Cordain L et al. Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr. 2005; 81(2):341-54.

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Ames BN. Low micronutrient intake may accelerate the degenerative diseases of aging through allocation of scarce micronutrients by triage. PNAS. 2006;103(47):17589-94.

Ames presents argument for eating more fruits/vegetables and taking key supplements:

- Multivitamin/mineral
- Magnesium (400-1000 mg)
- Fish oil (EPA/DHA) (1000-3000 mg)
- Vitamin D (2000-10,000 IU)
- a-Lipoic acid & acetyl-L-carnitine (ALCAR)
- Fiber

Seaman additions: CoQ10, botanicals, glucosamine/chondroitin, probiotics, calcium, chromium, vitamin C, iodine

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Researchers have identified that the DeFlame dietary approach is the best way to achieve a normal metabolic state. In fact, it is possible for obese individuals with a BMI as high as 36 to completely resolve the metabolic syndrome in just 12 weeks[10], and many were also able to completely resolve fatty liver disease with what the authors called the Spanish Mediterranean Ketogenic Diet.[11] Consider the anti-inflammatory foods that were consumed: olive oil, moderate red wine, green vegetables and salads, fish as the primary protein, as well as lean meat, fowl, eggs, shellfish, and cheese.[10-11] These foods form the foundation of the DeFlame Diet as outlined in Table 5, which also includes fruit, tubers, roots, and nuts.

Diet that creates a pro-inflammatory state	Diet that creates a DeFlamed state
Refined sugar	Grass-fed meat and wild game
Refined grains	Meats
Grain flour products	Wild-caught fish
Trans fats	Shellfish
Refined omega-6 seed oils (corn, safflower, sunflower, peanut, etc.)	Chicken
	Omega-3 eggs
	Cheese
	Vegetables
	Salads (leafy greens)
	Fruit
	Tubers/roots (potato, yams, sweet potato)
	Nuts (raw or dry roasted)
	Omega-3 seeds: hemp, chia, flax
	Dark chocolate
	Spices of all kinds
	Olive oil, coconut oil, butter, cream, avocado, bacon
	Red wine and stout beer
	Coffee and tea (green tea is best option)

A friend of mine reduced his A1c from 11% to 5.7% in 6 months.

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US had 2.5xs more people but 40xs more deaths vs Japan

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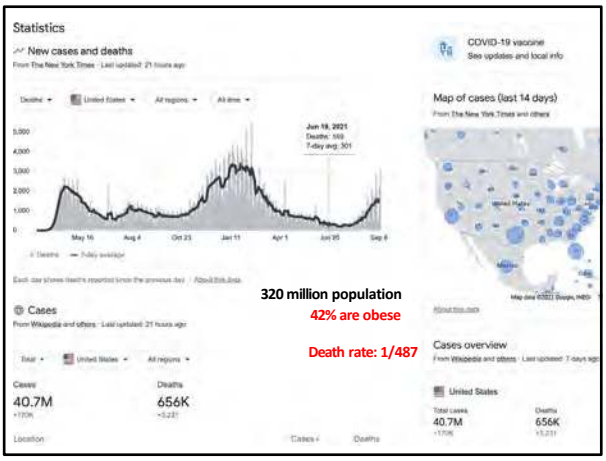

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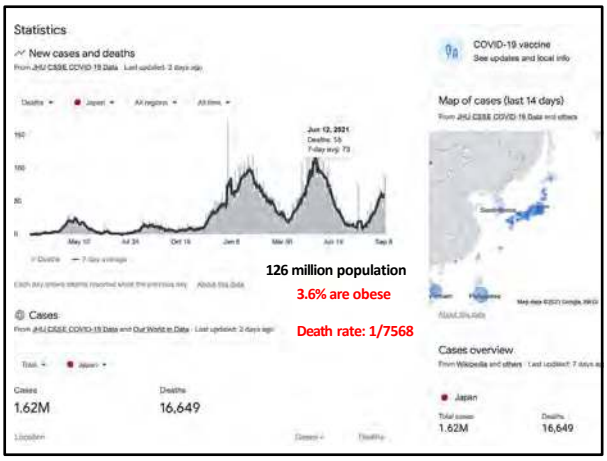

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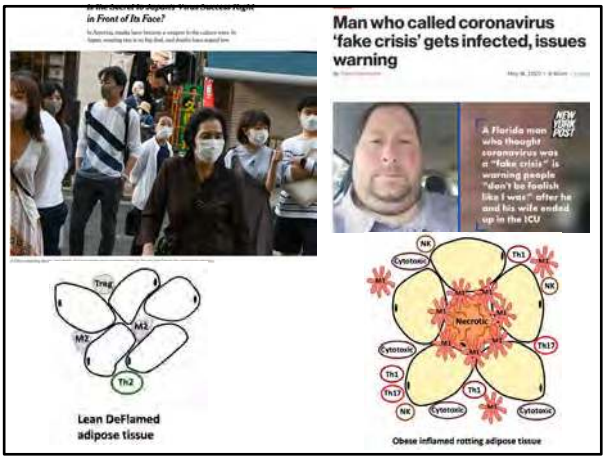

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COVID Stress Syndrome

How chronic stress trashes the brain

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Depress Anxiety. 2020 Aug;37(8):706-714. doi: 10.1002/da.23071. Epub 2020 Jul 5.

COVID stress syndrome: Concept, structure, and correlates

Steven Taylor[1] | Caeleigh A. Landry[2] | Michelle M. Paluszek[2] | Thomas A. Fergus[3] | Dean McKay[4] | Gordon J. G. Asmundson[2]

Abstract

Background: Research shows that the COVID Stress Scales have a robust multifactorial structure, representing five correlated facets of COVID-19-related distress: (a) Fear of the dangerousness of COVID-19, which includes fear of coming into contact with fomites potentially contaminated with SARSCoV2, (b) worry about socioeconomic costs of COVID-19 (e.g., worry about personal finances and disruption in the supply chain), (c) xenophobic fears that foreigners are spreading SARS-CoV2, (d) traumatic stress symptoms associated with direct or vicarious traumatic exposure to COVID-19 (nightmares, intrusive thoughts, or images related to COVID-19), and (e) COVID-19-related compulsive checking and reassurance seeking. These factors cohere to form a COVID stress syndrome, which we sought to further delineate in the present study.

Methods: A population-representative sample of 6,854 American and Canadian adults completed a self-report survey comprising questions about current mental

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Psychopharmacology (2002) 159:319–324
DOI 10.1007/s00213-001-0929-6

ORIGINAL INVESTIGATION

Stuart Brody · Ragnar Preut · Kerstin Schommer
Thomas H. Schürmeyer

A randomized controlled trial of high dose ascorbic acid for reduction of blood pressure, cortisol, and subjective responses to psychological stress

Received: 12 June 2001 / Accepted: 12 September 2001 / Published online: 20 November 2001
© Springer-Verlag 2001

Abstract *Rationale:* Physiological responses to stress are considered disruptive to health. High-dose ascorbic acid has reduced indices of stress in laboratory animals. *Methods:* We conducted a randomized double-blind, placebo-controlled 14-day trial of sustained-release ascorbic acid (60 healthy young adults; 3x1000 mg/day Cetebe) and placebo (60 healthy young adults) for reduction of blood pressure, cortisol, and subjective response to acute psychological stress (Trier Social Stress Test, TSST, consisting of public speaking and mental arithmetic). Six subjects from each group were excluded. *Results:* Compared to the placebo group, the ascorbic acid group had less systolic blood pressure (an increase of 23 versus

In this randomized controlled double-blind clinical trial, high-dose sustained-release ascorbic acid lessened the systolic and diastolic blood pressure, subjective stress, and state anxiety response to an acute interpersonal psychological stressor, and also produced faster recovery of salivary cortisol after the stressor.

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Stressed out people should consider taking 3000 mg or more of vitamin C.

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Review Article

Vitamin C: an essential "stress hormone" during sepsis

Paul E. Marik

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Correspondence to: Paul E. Marik, MD, FCCM, FCCP. Professor of Medicine, Chief, Pulmonary and Critical Care Medicine, Eastern Virginia Medical School, 825 Fairfax Ave. Suite 410, Norfolk, VA 23507, USA. Email: marikpe@evms.edu.

Abstract: The stress response is a preserved evolutionary response that functions to enhance the survival of the species. In mammals, the stress response is characterized by activation of the HPA axis and sympathoadrenal system (SAS) as well as the increased synthesis and secretion of vitamin C. Cortisol, catecholamines, and vitamin C act synergistically to increase hemodynamic reserve, maintain immune function and protect the host against excessive oxidant injury. Humans (and anthropoid apes) have lost the ability to synthesize vitamin C and therefore have an impaired stress response. The inability to produce vitamin C has serious implications in septic humans. Treatment with vitamin C appears to restore the stress response and improve the survival of stressed humans.

Keywords: Sepsis, vitamin C, HPA axis, stress response

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View this article at: http://dx.doi.org/10.21037/jtd.2019.12.84

J Thorac Dis. **2020;12(Suppl 1):S84-S88**

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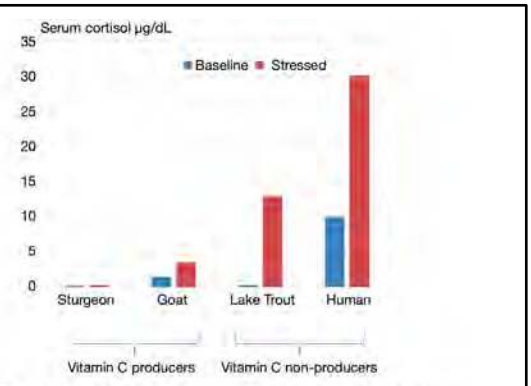

Figure 1 Graphical display of baseline cortisol and cortisol stress response in representative fish and mammals.

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Received: 12 May 2020 | Revised: 13 June 2020 | Accepted: 13 June 2020
DOI: 10.1002/da.23071

RESEARCH ARTICLE

Depress Anxiety. 2020 Aug;37(8):706-714. doi: 10.1002/da.23071. Epub 2020 Jul 5.

COVID stress syndrome: Concept, structure, and correlates

1. **Fear of the dangerousness of COVID-19**
2. **Worry about socioeconomic costs of COVID-19 (e.g., worry about personal finances and disruption in the supply chain)**
3. **Xenophobic fears that foreigners are spreading SARS-CoV2**
4. **Traumatic stress symptoms (COVID PTSD), such as nightmares, intrusive thoughts, or images related to COVID- 19**
5. **COVID-19-related compulsive checking and reassurance seeking**

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Americans overestimate risk of death by more than 5000%

- Americans believe that people aged 44 and younger account for about 30% of total deaths; the actual figure is 2.7%.
- Americans overestimate the risk of death from COVID-19 for people aged 24 and younger by a factor of 50; and they think the risk for people aged 65 and older is half of what it actually is (40% vs 80%).

These results are nothing short of stunning. Mortality data have shown from the very beginning that the COVID-19 virus age-discriminates, with deaths overwhelmingly concentrated in people who are older and suffer comorbidities. This is perhaps the only uncontroversial piece of evidence we have about this virus. Nearly all US fatalities have been among people older than 55; and yet a large number of Americans are still convinced that the risk to those younger than 55 is almost the same as to those who are older.

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News in focus

THE CORONAVIRUS IS MOST DEADLY IF YOU ARE OLD AND MALE

A slew of detailed studies has now quantified the increased risk the virus poses for various groups.

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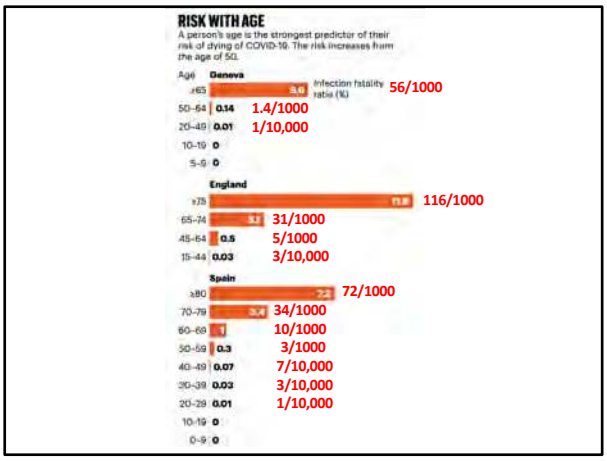

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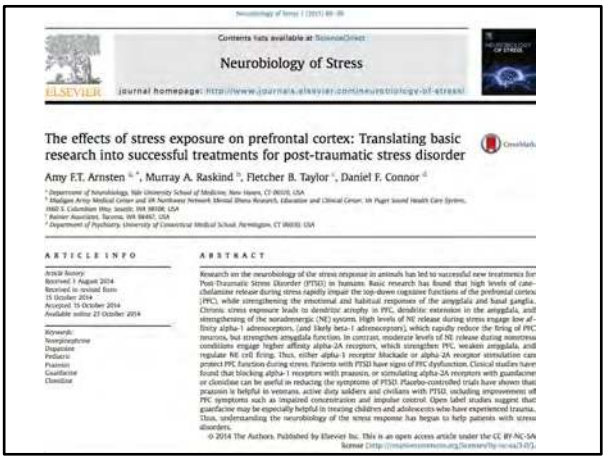

The effects of stress exposure on prefrontal cortex: Translating basic research into successful treatments for post-traumatic stress disorder

Amy F.T. Arnsten, Murray A. Raskind, Fletcher B. Taylor, Daniel F. Connor

ARTICLE INFO

ABSTRACT

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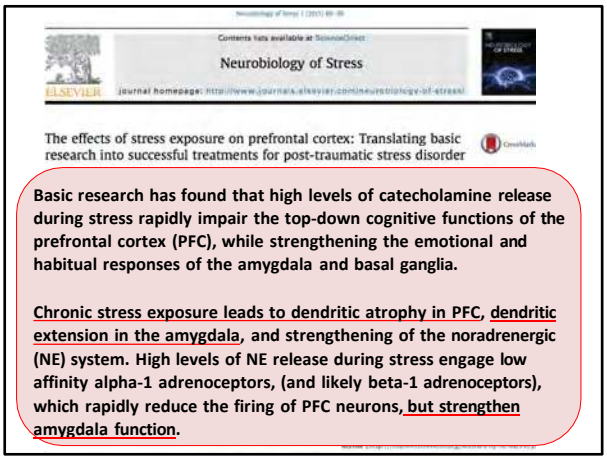

The effects of stress exposure on prefrontal cortex: Translating basic research into successful treatments for post-traumatic stress disorder

Basic research has found that high levels of catecholamine release during stress rapidly impair the top-down cognitive functions of the prefrontal cortex (PFC), while strengthening the emotional and habitual responses of the amygdala and basal ganglia.

Chronic stress exposure leads to dendritic atrophy in PFC, dendritic extension in the amygdala, and strengthening of the noradrenergic (NE) system. High levels of NE release during stress engage low affinity alpha-1 adrenoceptors, (and likely beta-1 adrenoceptors), which rapidly reduce the firing of PFC neurons, but strengthen amygdala function.

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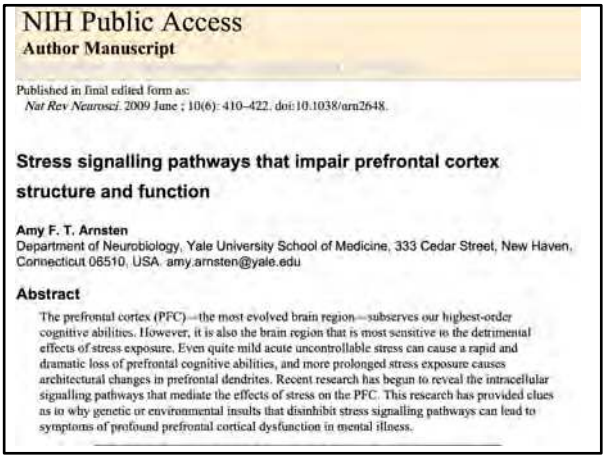

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Stress signalling pathways that impair prefrontal cortex structure and function

Amy F. T. Arnsten
Department of Neurobiology, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510, USA. amy.arnsten@yale.edu

Abstract

The prefrontal cortex (PFC)—the most evolved brain region—subserves our highest-order cognitive abilities. However, it is also the brain region that is most sensitive to the detrimental effects of stress exposure. Even quite mild acute uncontrollable stress can cause a rapid and dramatic loss of prefrontal cognitive abilities, and more prolonged stress exposure causes architectural changes in prefrontal dendrites. Recent research has begun to reveal the intracellular signalling pathways that mediate the effects of stress on the PFC. This research has provided clues as to why genetic or environmental insults that disinhibit stress signalling pathways can lead to symptoms of profound prefrontal cortical dysfunction in mental illness.

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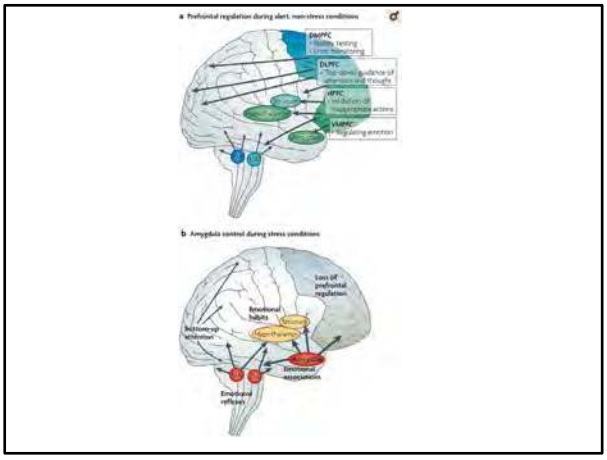

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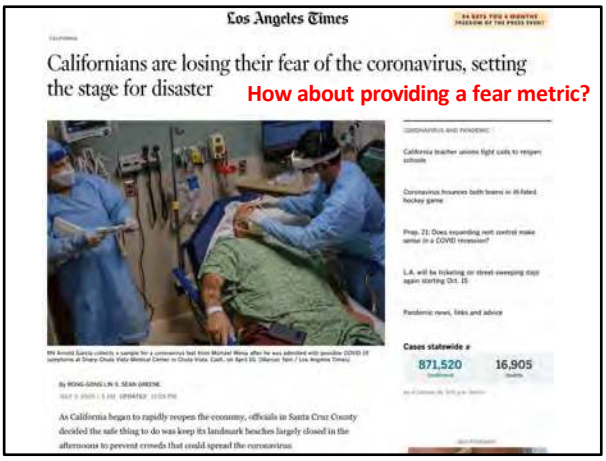

Los Angeles Times

Californians are losing their fear of the coronavirus, setting the stage for disaster

How about providing a fear metric?

Cases statewide

871,520 16,905

As California began to rapidly reopen the economy, officials in Santa Cruz County decided the safe thing to do was keep its landmark beaches largely closed in the afternoons to prevent crowds that could spread the coronavirus

43


Medscape

'Staggering' Doubling of Type 2 Diabetes in Kids During Pandemic

Recommendations

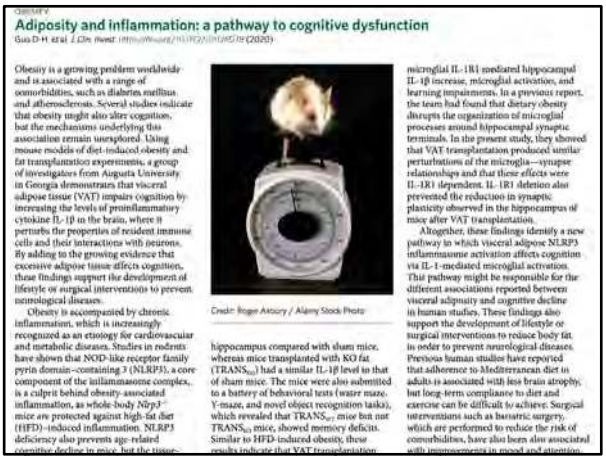
This incidence of type 2 diabetes in children appears to have doubled during the COVID-19 pandemic, data from two new US studies suggest, with the lead investigator of one saying she was "surprised by the staggering increase in cases of type 2 diabetes...and the increase in severity of presentation."

Findings from the two separate retrospective chart reviews — one conducted in Washington, DC, and the other in Baton Rouge, Louisiana — were presented June 25 at the virtual American Diabetes Association (ADA) 81st Scientific Sessions.

Although the two studies differed somewhat in the clinical parameters examined, both revealed a similar doubling of the rates of hospitalizations for type 2 diabetes among youth during 2020 compared with the same time period in 2019, as well as greater severity of metabolic disturbance.

And, as has been previously described with type 2 diabetes in youth, African-American ethnicity predominated in both cohorts.

44


Adiposity and inflammation: a pathway to cognitive dysfunction

Obesity is a growing problem worldwide and is associated with a range of comorbidities, such as diabetes mellitus and atherosclerosis. Several studies indicate that obesity might also alter cognition, but the mechanisms underlying this association remain unexplored. Using mouse models of diet-induced obesity and fat transplantation experiments, a group of investigators from Augusta University in Georgia demonstrates that visceral adipose tissue (VAT) impairs cognition by increasing the levels of proinflammatory cytokine IL-1β in the brain, where it perturbs the properties of resident immune cells and their interactions with neurons. By adding to the growing evidence that excessive adipose tissue affects cognition, these findings support the development of lifestyle or surgical interventions to prevent neurological diseases.

Obesity is accompanied by chronic inflammation, which is increasingly recognized as an etiology for cardiovascular and metabolic diseases. Studies in rodents have shown that NOD-like receptor family pyrin domain–containing 3 (NLRP3), a core component of the inflammasome complex, is a culprit behind obesity-associated inflammation, as whole-body *Nlrp3*$^{-/-}$ mice are protected against high-fat diet (HFD)–induced inflammation. NLRP3 deficiency also prevents age-related cognitive decline in mice, but the tissue-

Credit: Roger Ressmeyer / Alamy Stock Photo

hippocampus compared with sham mice, whereas mice transplanted with KO fat ($TRANS_{KO}$) had a similar IL-1β level to that of sham mice. The mice were also submitted to a battery of behavioral tests (water maze, Y-maze, and novel object recognition tasks), which revealed that $TRANS_{KO}$ mice but not $TRANS_{WT}$ mice, showed memory deficits. Similar to HFD-induced obesity, these results indicate that VAT transplantation

microglial IL-1R1 mediated hippocampal IL-1β increase, microglial activation, and learning impairments. In a previous report, the team had found that dietary obesity disrupts the organization of microglial processes around hippocampal synaptic terminals. In the present study, they showed that VAT transplantation produced similar perturbations of the microglia—synapse relationships and that these effects were IL-1R1 dependent. IL-1R1 deletion also prevented the reduction in synaptic plasticity observed in the hippocampus of mice after VAT transplantation.

Altogether, these findings identify a new pathway by which visceral adipose NLRP3 inflammasome activation affects cognition via IL-1–mediated microglial activation. This pathway might be responsible for the different associations reported between visceral adiposity and cognitive decline in human studies. These findings also support the development of lifestyle or surgical interventions to reduce body fat in order to prevent neurological diseases. Previous human studies have reported that adherence to Mediterranean diet in adults is associated with less brain atrophy, but long-term compliance to diet and exercise can be difficult to achieve. Surgical interventions such as bariatric surgery, which are performed to reduce the risk of comorbidities, have also been also associated with improvements in mood and attention

45

The cause of all chronic diseases

46

One group of DCs claim ben… adju… phys… …quate …ence.

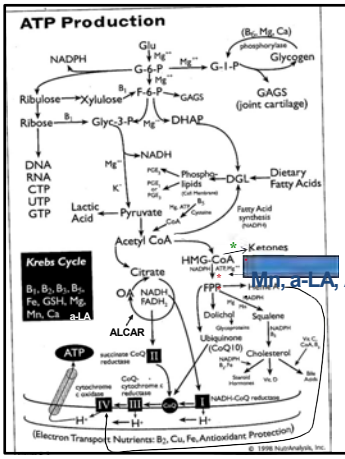
Example of symptoms caused by hypocapnia = respiratory alkalosis:

- apprehension
- faintness
- fatigue
- headache
- impaired concentration
- giddiness
- irritability
- seizure
- weakness
- visual disturbances
- diaphoresis
- perioral numbness
- dyspnea
- palpations
- tachycardia
- abdominal discomfort
- chest pain
- air swallowing
- breathlessness
- yawning and/or sighing
- dry mouth
- tetany
- muscle tightening & stiffness
- distal paresthesias

1. Duncan B, Raffin T. Handling hyperventilation syndrome. Hosp Med. 1992;28:58-67.
2. Rice RL. Symptom patterns of the hyperventilation syndrome. Am J Med. 1950;8:691-700.

Ano… …e that … good for back pain.

47



ATP synthesis

Glycolysis: Mg++

Krebs: B-vitamins, Mg, Fe, Mn, a-LA, ALCAR

Insulin stimulates

Statins inhibit

Electron transport: CoQ10, a-LA, Heme A (B2, B5, B6, biotiin, iron, copper, zinc)

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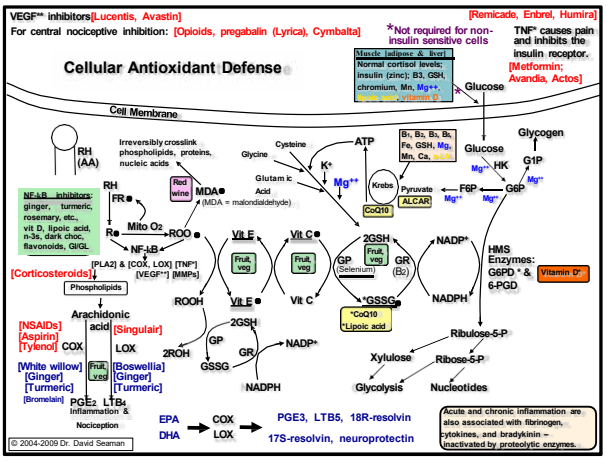

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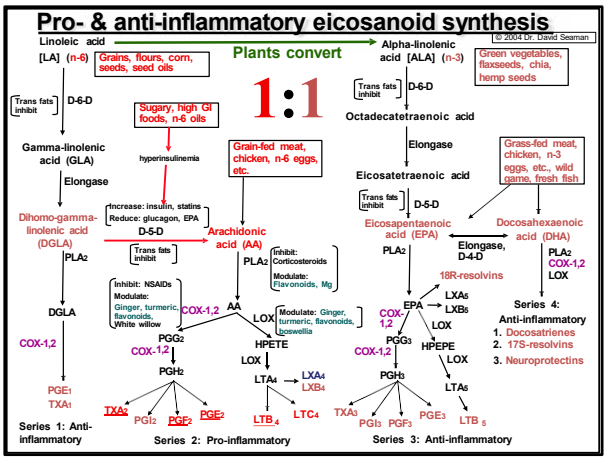

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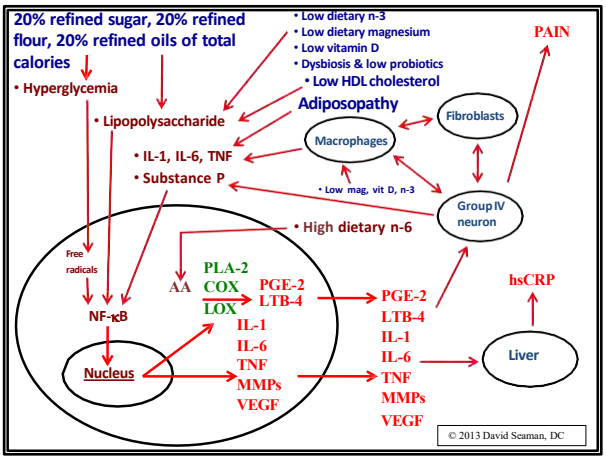

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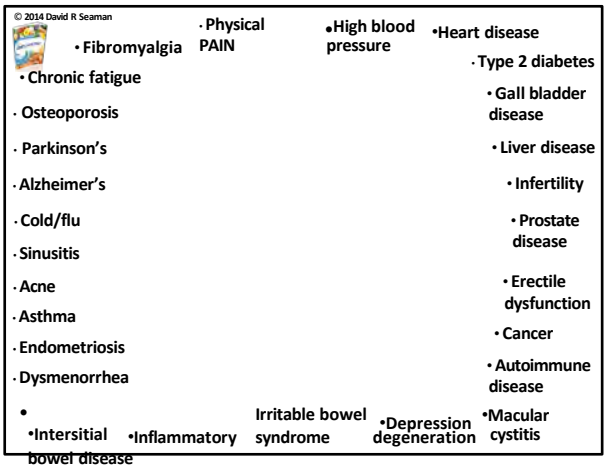

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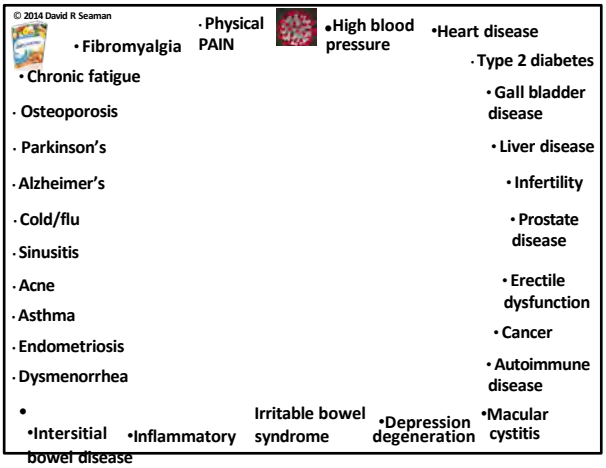

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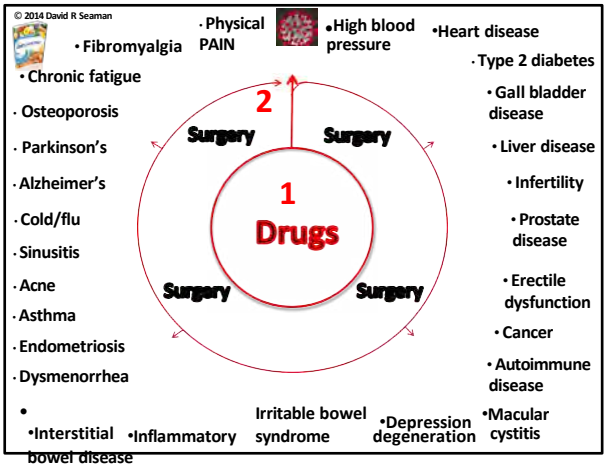

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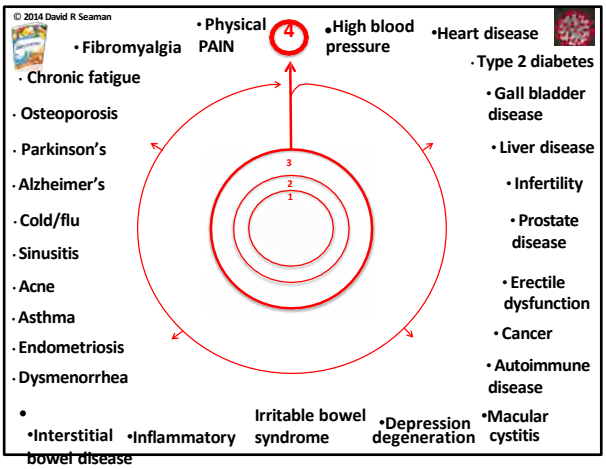

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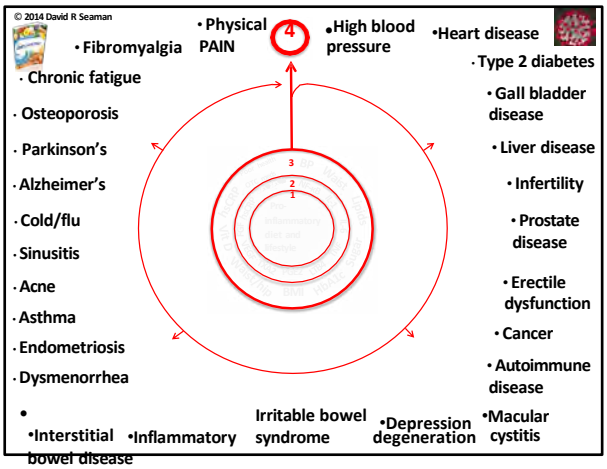

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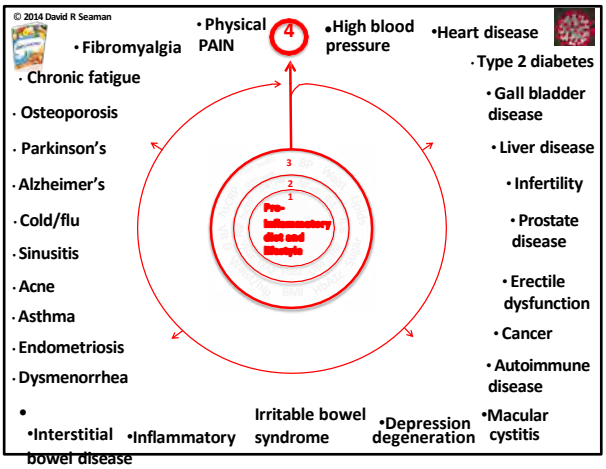

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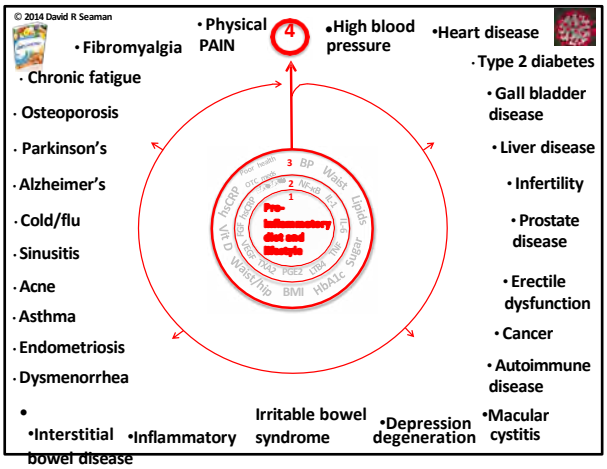

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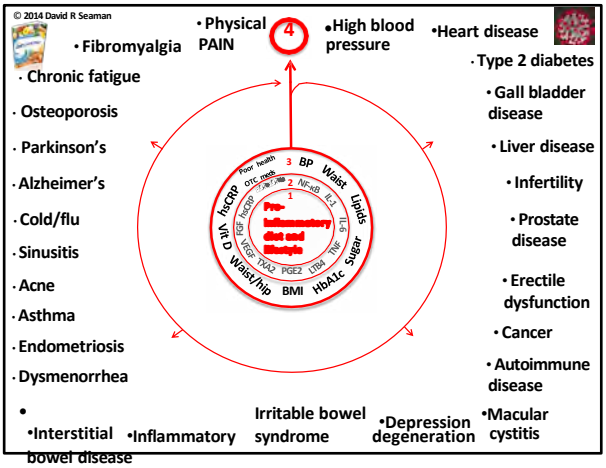

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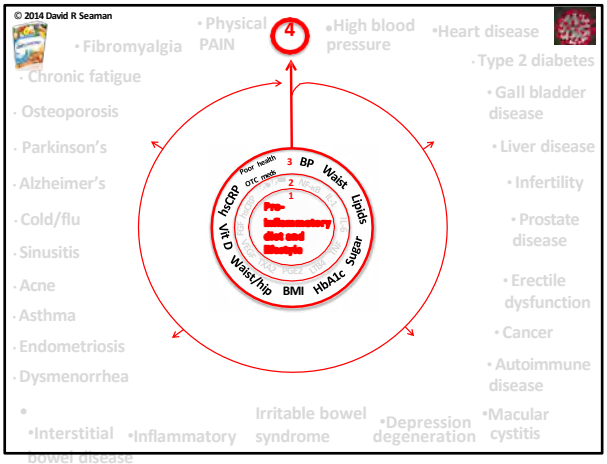

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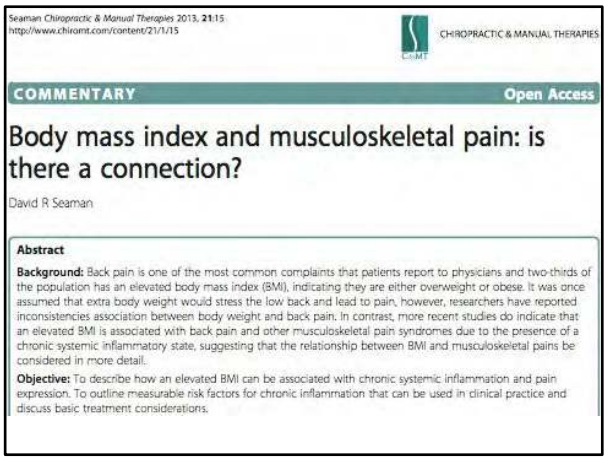

Seaman *Chiropractic & Manual Therapies* 2013, **21**:15
http://www.chiromt.com/content/21/1/15

CHIROPRACTIC & MANUAL THERAPIES

COMMENTARY Open Access

Body mass index and musculoskeletal pain: is there a connection?

David R Seaman

Abstract

Background: Back pain is one of the most common complaints that patients report to physicians and two-thirds of the population has an elevated body mass index (BMI), indicating they are either overweight or obese. It was once assumed that extra body weight would stress the low back and lead to pain, however, researchers have reported inconsistencies association between body weight and back pain. In contrast, more recent studies do indicate that an elevated BMI is associated with back pain and other musculoskeletal pain syndromes due to the presence of a chronic systemic inflammatory state, suggesting that the relationship between BMI and musculoskeletal pains be considered in more detail.

Objective: To describe how an elevated BMI can be associated with chronic systemic inflammation and pain expression. To outline measurable risk factors for chronic inflammation that can be used in clinical practice and discuss basic treatment considerations.

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Table 2 Pro-inflammatory chemistry of the metabolic syndrome

Hyperglycemia	↑ NF-κB
Hyperinsulinemia	↑ CRP
Hypertriglyceridemia	↑ TNF
Hyperuricemia	↑ IL-6
↓ HDL	↑ Increased white blood cell count
↓ protein synthesis	↑ plasminogen activator inhibitor
↑ protein catabolism	↑ Fibrinogen
↑ gluconeogenesis	↑ Leptin
↑ serum amyloid A	↑ Resistin
↑ angiotensinogen	↓ adiponectin

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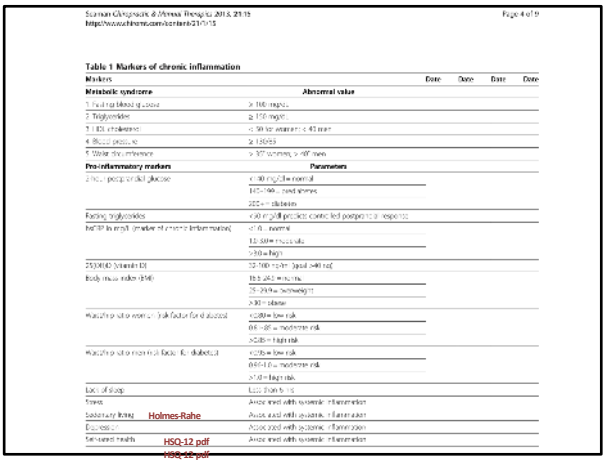


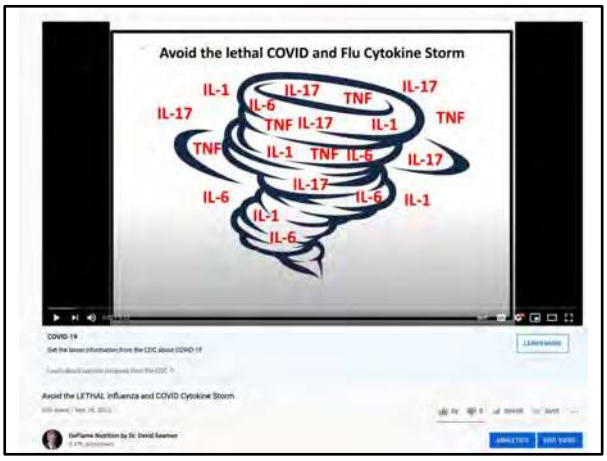
Seaman Chiropractic & Manual Therapies 2013, 21:15
http://www.chiromt.com/content/21/1/15

Page 4 of 9

Table 1 Markers of chronic inflammation

Markers	Done	Done	Done	Done
Metabolic syndrome	**Abnormal value**			
1. Fasting blood glucose	> 100 mg/dL			
2. Triglycerides	≥ 150 mg/dL			
3. HDL cholesterol	< 50 for women; < 40 men			
4. Blood pressure	≥ 130/85			
5. Waist circumference	> 37" women; > 40" men			
Pro-inflammatory markers	**Parameters**			
1. Hemoglobin A1c/ fasting blood glucose	< 5.7% = normal 5.7–6.4 = pre-diabetes ≥ 6.5 = diabetes			
Fasting triglycerides	< 90 mg/dl provide controlled postprandial response			
hsCRP (marker of chronic inflammation)	< 1.0 = normal 1.0–3.0 = moderate risk > 3.0 = high risk			
25(OH)D Vitamin D	32–100 ng/ml = good; >40 ng/ml			
Body mass index (BMI)	18.5–24.9 = healthy 25–29.9 = overweight > 30 = obese			
Waist/hip ratio (central adiposity risk factor for disease)	< 0.80 = low risk 0.8 –.85 = moderate risk > 0.85 = high risk			
Waist/height ratio (central adiposity risk factor for diabetes)	< 0.5 = low risk 0.51–1.0 = moderate risk > 1.0 = high risk			
Lack of sleep	Less than 6 hrs			
Stress	Associated with systemic inflammation			
Sedentary living Holmes-Rahe	Associated with systemic inflammation			
Depression	Associated with systemic inflammation			
Self-rated health HSQ-12.pdf HSQ-12.pdf	Associated with systemic inflammation			

63



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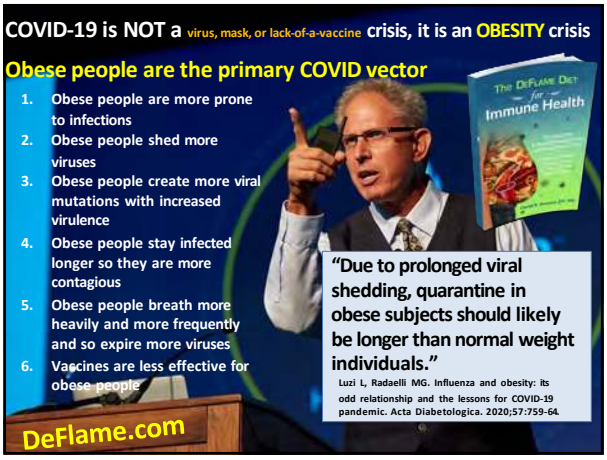
Don't Be Ashamed of Those Extra Pounds

Why your extra COVID-19 pounds makes you a walking talking coronavirus spreading machine

65



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Asymptomatic spread of coronavirus is 'very rare,' WHO says

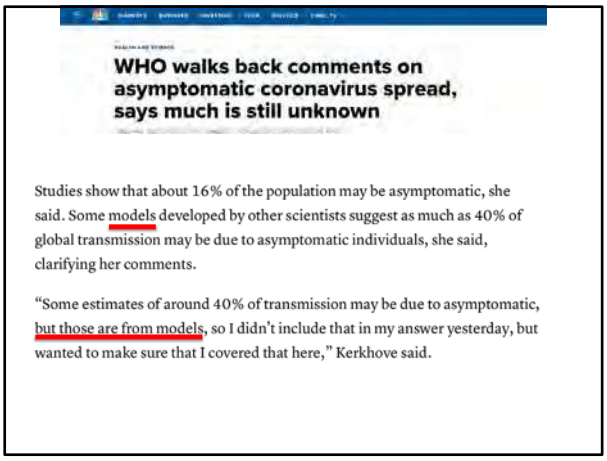
KEY POINTS

#AloneTogether

WHO: Coronavirus patients who don't show symptoms aren't driving the spread of the virus

TRENDING NOW

67



WHO walks back comments on asymptomatic coronavirus spread, says much is still unknown

Studies show that about 16% of the population may be asymptomatic, she said. Some models developed by other scientists suggest as much as 40% of global transmission may be due to asymptomatic individuals, she said, clarifying her comments.

"Some estimates of around 40% of transmission may be due to asymptomatic, but those are from models, so I didn't include that in my answer yesterday, but wanted to make sure that I covered that here," Kerkhove said.

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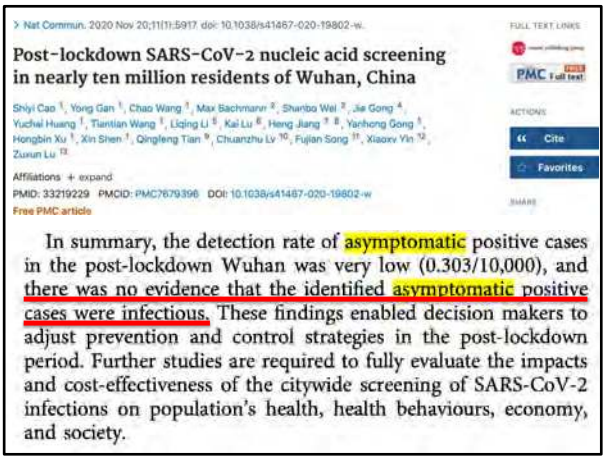

> Nat Commun. 2020 Nov 20;11(1):5917. doi: 10.1038/s41467-020-19802-w.

Post-lockdown SARS-CoV-2 nucleic acid screening in nearly ten million residents of Wuhan, China

Shiyi Cao [1], Yong Gan [1], Chao Wang [1], Max Bachmann [2], Shanbo Wei [3], Jie Gong [4], Yuchai Huang [1], Tiantian Wang [1], Liqing Li [5], Kai Lu [6], Heng Jiang [7, 8], Yanhong Gong [1], Hongbin Xu [1], Xin Shen [1], Qingfeng Tian [9], Chuanzhu Lv [10], Fujian Song [11], Xiaoxv Yin [12], Zuxun Lu [13]

Affiliations + expand

PMID: 33219229 PMCID: PMC7679396 DOI: 10.1038/s41467-020-19802-w

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In summary, the detection rate of asymptomatic positive cases in the post-lockdown Wuhan was very low (0.303/10,000), and there was no evidence that the identified asymptomatic positive cases were infectious. These findings enabled decision makers to adjust prevention and control strategies in the post-lockdown period. Further studies are required to fully evaluate the impacts and cost-effectiveness of the citywide screening of SARS-CoV-2 infections on population's health, health behaviours, economy, and society.

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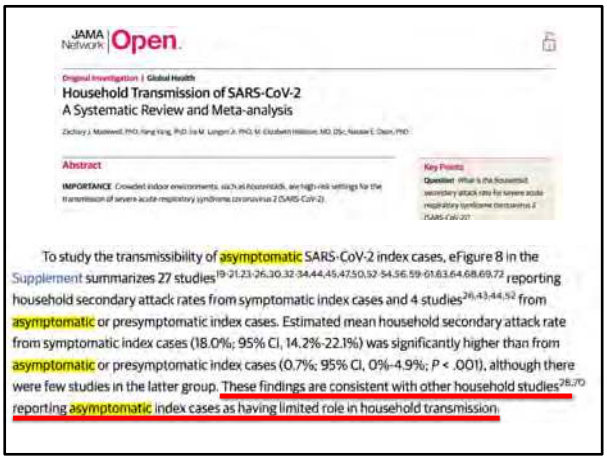

JAMA Network Open.

Original Investigation | Global Health

Household Transmission of SARS-CoV-2 A Systematic Review and Meta-analysis

Abstract

Key Points

To study the transmissibility of asymptomatic SARS-CoV-2 index cases, eFigure 8 in the Supplement summarizes 27 studies[19-21,23-26,30,32-34,44,45,47,50,52-54,56,59-61,63,64,68,69,72] reporting household secondary attack rates from symptomatic index cases and 4 studies[26,43,44,52] from asymptomatic or presymptomatic index cases. Estimated mean household secondary attack rate from symptomatic index cases (18.0%; 95% CI, 14.2%-22.1%) was significantly higher than from asymptomatic or presymptomatic index cases (0.7%; 95% CI, 0%-4.9%; $P < .001$), although there were few studies in the latter group. These findings are consistent with other household studies[28,70] reporting asymptomatic index cases as having limited role in household transmission.

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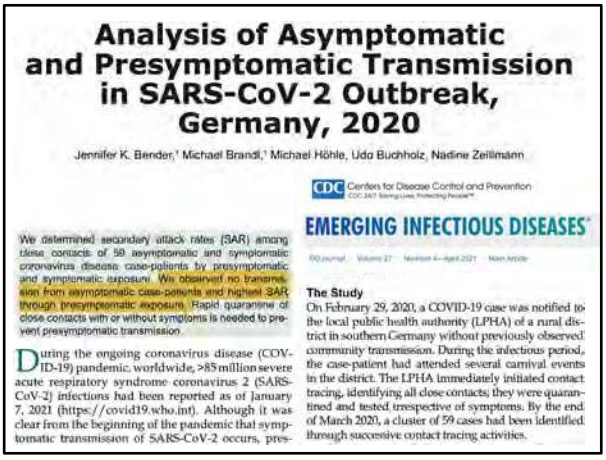

Analysis of Asymptomatic and Presymptomatic Transmission in SARS-CoV-2 Outbreak, Germany, 2020

Jennifer K. Bender,[1] Michael Brandl,[1] Michael Höhle, Udo Buchholz, Nadine Zeilmann

CDC Centers for Disease Control and Prevention

EMERGING INFECTIOUS DISEASES

We determined secondary attack rates (SAR) among close contacts of 59 asymptomatic and symptomatic coronavirus disease case-patients by presymptomatic and symptomatic exposure. We observed no transmission from asymptomatic case-patients and highest SAR through presymptomatic exposure. Rapid quarantine of close contacts with or without symptoms is needed to prevent presymptomatic transmission.

During the ongoing coronavirus disease (COVID-19) pandemic, worldwide, >85 million severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections had been reported as of January 7, 2021 (https://covid19.who.int). Although it was clear from the beginning of the pandemic that symptomatic transmission of SARS-CoV-2 occurs, pres-

The Study

On February 29, 2020, a COVID-19 case was notified to the local public health authority (LPHA) of a rural district in southern Germany without previously observed community transmission. During the infectious period, the case-patient had attended several carnival events in the district. The LPHA immediately initiated contact tracing, identifying all close contacts; they were quarantined and tested irrespective of symptoms. By the end of March 2020, a cluster of 59 cases had been identified through successive contact tracing activities.

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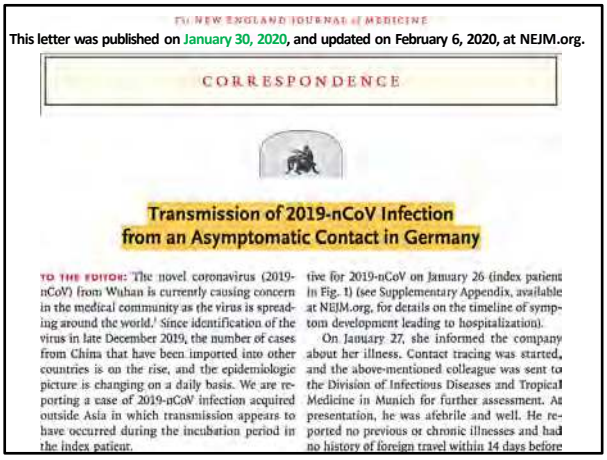


THE NEW ENGLAND JOURNAL of MEDICINE

This letter was published on January 30, 2020, and updated on February 6, 2020, at NEJM.org.

CORRESPONDENCE

Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany

TO THE EDITOR: The novel coronavirus (2019-nCoV) from Wuhan is currently causing concern in the medical community as the virus is spreading around the world.[1] Since identification of the virus in late December 2019, the number of cases from China that have been imported into other countries is on the rise, and the epidemiologic picture is changing on a daily basis. We are reporting a case of 2019-nCoV infection acquired outside Asia in which transmission appears to have occurred during the incubation period in the index patient.

tive for 2019-nCoV on January 26 (index patient in Fig. 1) (see Supplementary Appendix, available at NEJM.org, for details on the timeline of symptom development leading to hospitalization).

On January 27, she informed the company about her illness. Contact tracing was started, and the above-mentioned colleague was sent to the Division of Infectious Diseases and Tropical Medicine in Munich for further assessment. At presentation, he was afebrile and well. He reported no previous or chronic illnesses and had no history of foreign travel within 14 days before

72

This letter was published on January 30, 2020, and updated on February 6, 2020, at NEJM.org.

Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany

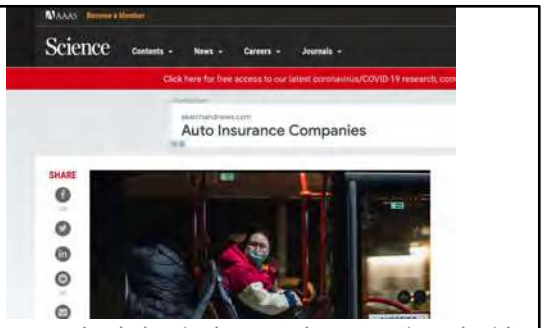
Before the onset of symptoms, he had attended meetings with a Chinese business partner at his company near Munich on January 20 and 21. The business partner, a Shanghai resident, had visited Germany between January 19 and 22. During her stay, she had been well with no signs or symptoms of infection but had become ill on her flight back to China, where she tested posi-

73

Letter to editor

~~Study~~ claiming new coronavirus can be transmitted by people without symptoms was flawed

74



Chinese researchers had previously suggested asymptomatic people might transmit the virus but had not presented clear-cut evidence. "There's no doubt after reading [the *NEJM*] ~~letter~~ that asymptomatic transmission is occurring," Anthony Fauci, director of the U.S. National Institute of Allergy and Infectious Diseases, told journalists. "This ~~study~~ lays the question to rest."

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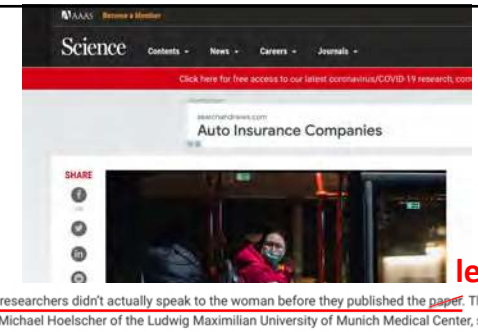

letter

But the researchers didn't actually speak to the woman before they published the ~~paper~~. The last author, Michael Hoelscher of the Ludwig Maximilian University of Munich Medical Center, says the paper relied on information from the four other patients: "They told us that the patient from China did not appear to have any symptoms." Afterward, however, RKI and the Health and Food Safety Authority of the state of Bavaria did talk to the Shanghai patient on the phone, and it turned out she did have symptoms while in Germany. According to people familiar with the call, she felt tired, suffered from muscle pain, and took paracetamol, a fever-lowering medication. (An RKI spokesperson would only confirm to *Science* that the woman had symptoms.)

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Letter to editor

~~Study~~ claiming new coronavirus can be transmitted by people without symptoms was flawed

By Kai Kupferschmidt | Feb. 3, 2020 , 5:30 PM

Asymptomatic transmission yet to be demonstrated as of June, 2020

***Update, 2 June, 7:20 p.m.:** This story has been cited widely on social media to argue against the use of face masks and shelter-in-place policies. This is based on a misreading of the article. The fact that the* New England Journal of Medicine *~~paper~~ had a flaw does not mean asymptomatic transmission (by people who have absolutely no symptoms) does not exist, this is still under discussion. But it is now well-established that people with very mild symptoms—so mild they are unlikely to recognize them as COVID-19—can infect others and even spark large outbreaks of disease.*

~~letter~~

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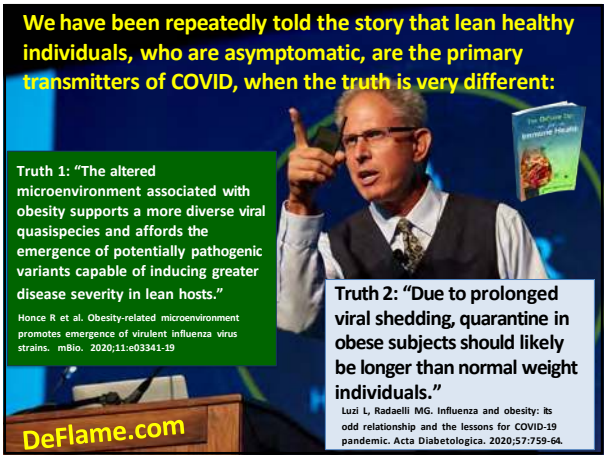

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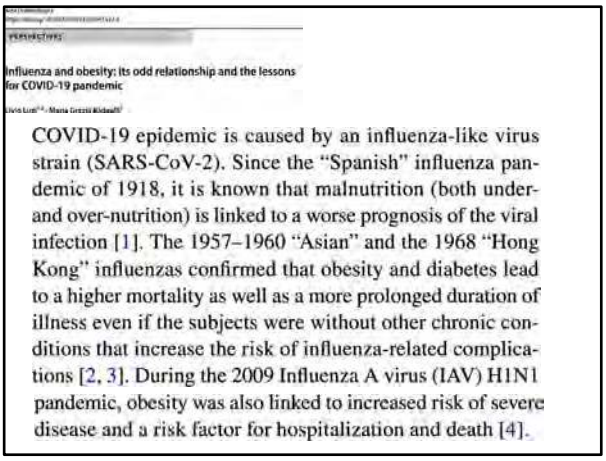

PERSPECTIVES

Influenza and obesity: its odd relationship and the lessons for COVID-19 pandemic

COVID-19 epidemic is caused by an influenza-like virus strain (SARS-CoV-2). Since the "Spanish" influenza pandemic of 1918, it is known that malnutrition (both under- and over-nutrition) is linked to a worse prognosis of the viral infection [1]. The 1957–1960 "Asian" and the 1968 "Hong Kong" influenzas confirmed that obesity and diabetes lead to a higher mortality as well as a more prolonged duration of illness even if the subjects were without other chronic conditions that increase the risk of influenza-related complications [2, 3]. During the 2009 Influenza A virus (IAV) H1N1 pandemic, obesity was also linked to increased risk of severe disease and a risk factor for hospitalization and death [4].

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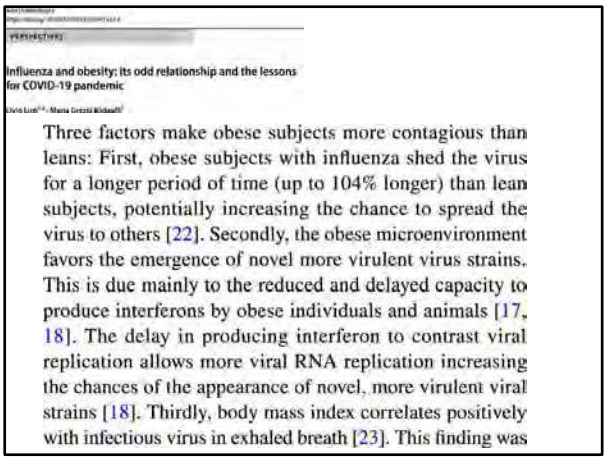

PERSPECTIVES

Influenza and obesity: its odd relationship and the lessons for COVID-19 pandemic

Three factors make obese subjects more contagious than leans: First, obese subjects with influenza shed the virus for a longer period of time (up to 104% longer) than lean subjects, potentially increasing the chance to spread the virus to others [22]. Secondly, the obese microenvironment favors the emergence of novel more virulent virus strains. This is due mainly to the reduced and delayed capacity to produce interferons by obese individuals and animals [17, 18]. The delay in producing interferon to contrast viral replication allows more viral RNA replication increasing the chances of the appearance of novel, more virulent viral strains [18]. Thirdly, body mass index correlates positively with infectious virus in exhaled breath [23]. This finding was

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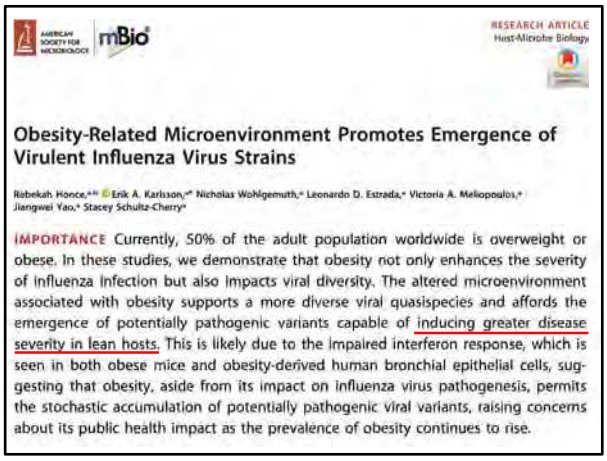

AMERICAN SOCIETY FOR MICROBIOLOGY | mBio

RESEARCH ARTICLE
Host-Microbe Biology

Obesity-Related Microenvironment Promotes Emergence of Virulent Influenza Virus Strains

Rebekah Honce,[a,b] Erik A. Karlsson,[c#] Nicholas Wohlgemuth,[a] Leonardo D. Estrada,[a] Victoria A. Meliopoulos,[a] Jiangwei Yao,[a] Stacey Schultz-Cherry[a]

IMPORTANCE Currently, 50% of the adult population worldwide is overweight or obese. In these studies, we demonstrate that obesity not only enhances the severity of influenza infection but also impacts viral diversity. The altered microenvironment associated with obesity supports a more diverse viral quasispecies and affords the emergence of potentially pathogenic variants capable of inducing greater disease severity in lean hosts. This is likely due to the impaired interferon response, which is seen in both obese mice and obesity-derived human bronchial epithelial cells, suggesting that obesity, aside from its impact on influenza virus pathogenesis, permits the stochastic accumulation of potentially pathogenic viral variants, raising concerns about its public health impact as the prevalence of obesity continues to rise.

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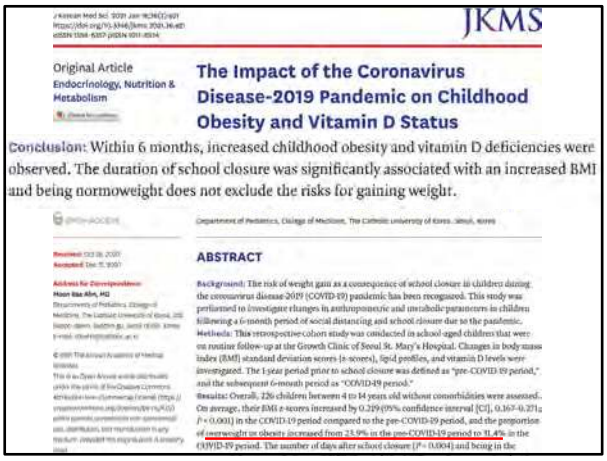

JKMS

Original Article
Endocrinology, Nutrition & Metabolism

The Impact of the Coronavirus Disease-2019 Pandemic on Childhood Obesity and Vitamin D Status

Conclusion: Within 6 months, increased childhood obesity and vitamin D deficiencies were observed. The duration of school closure was significantly associated with an increased BMI and being normoweight does not exclude the risks for gaining weight.

ABSTRACT

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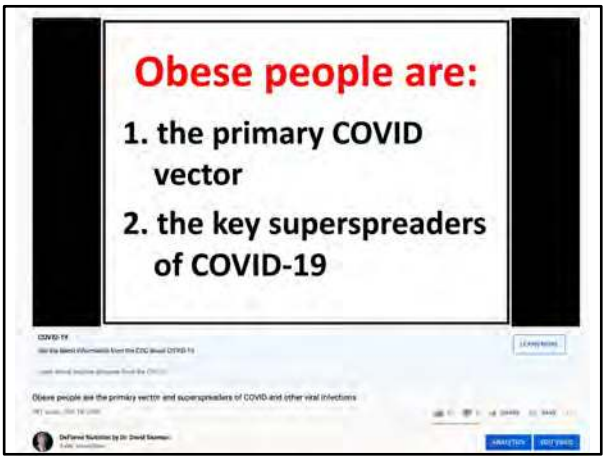

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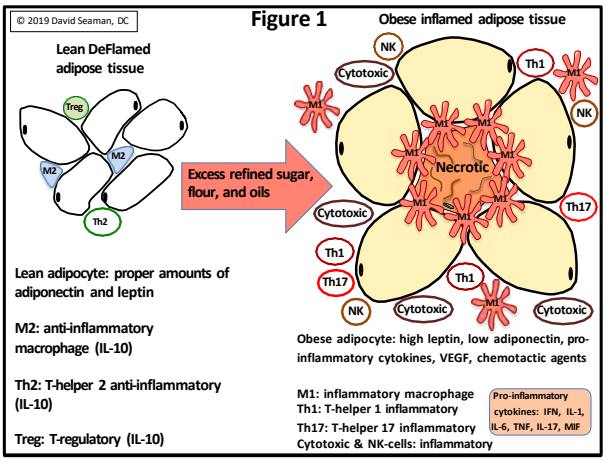

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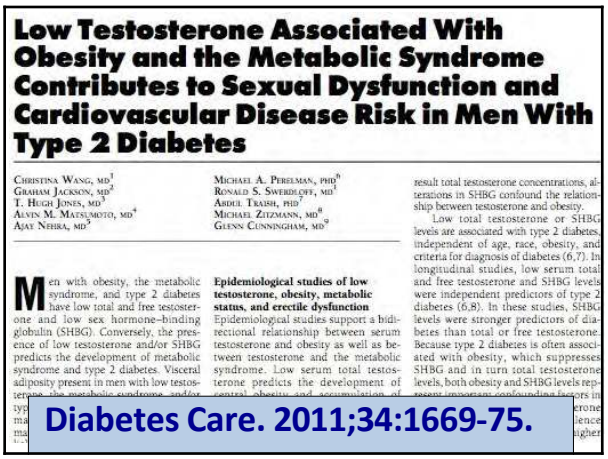

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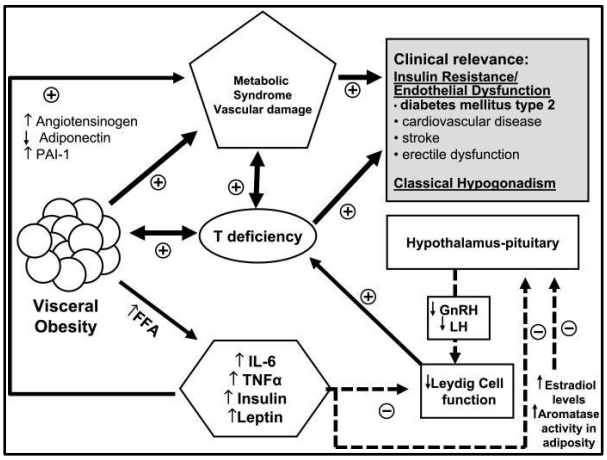

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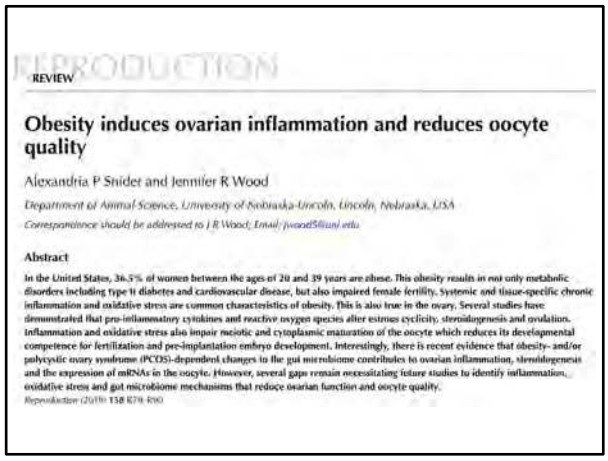

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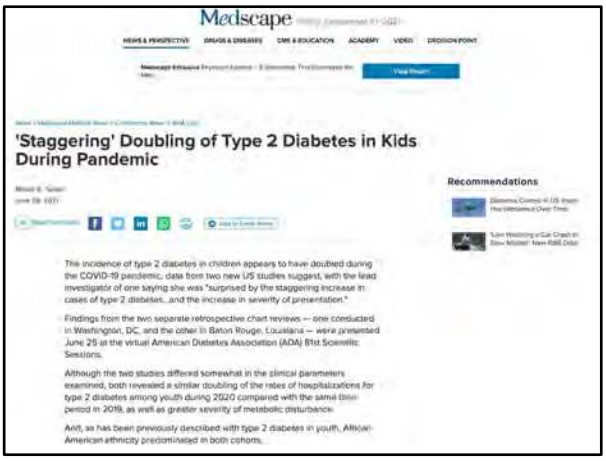

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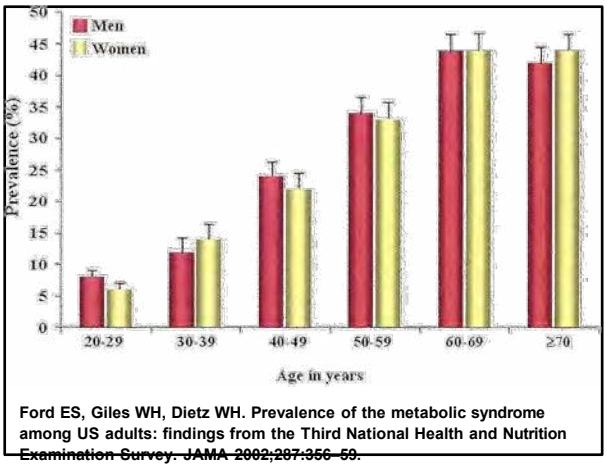

Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey. JAMA 2002;287:356–59.

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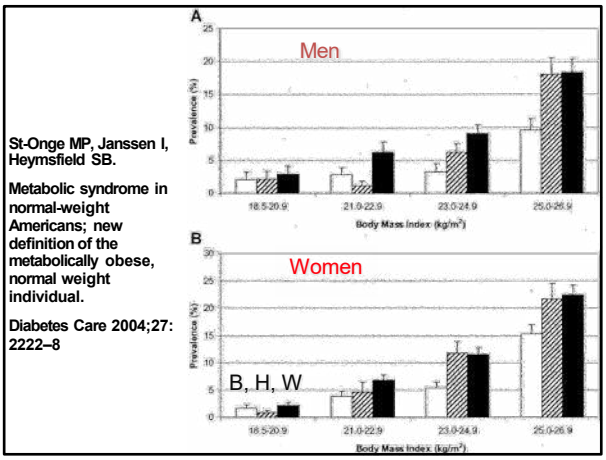

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Metabolic syndrome in normal-weight Americans; new definition of the metabolically obese, normal weight individual.

Diabetes Care 2004;27: 2222–8

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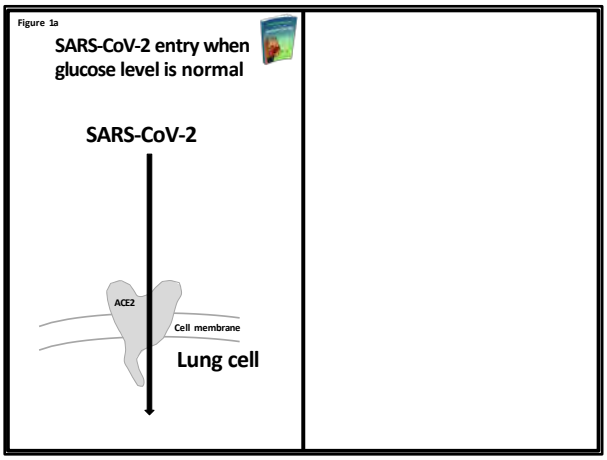

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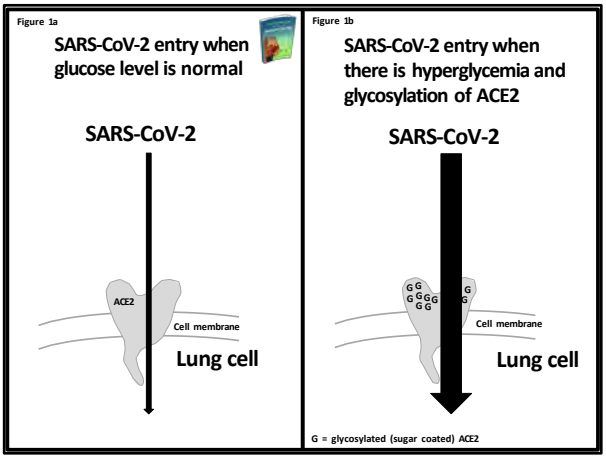

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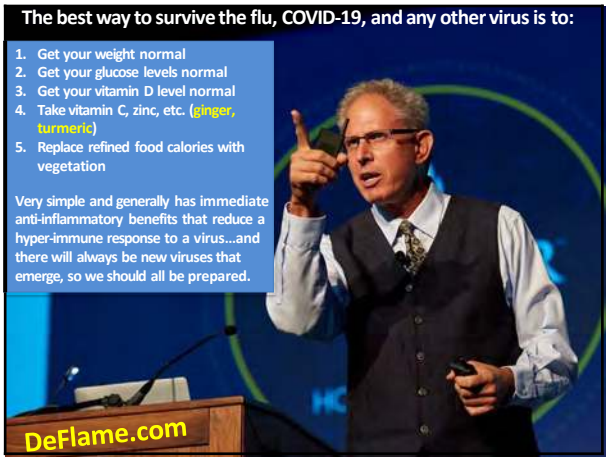

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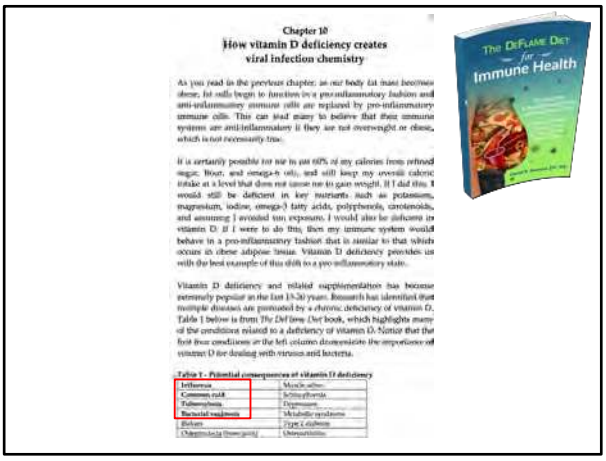

Chapter 10

How vitamin D deficiency creates viral infection chemistry

As you read in the previous chapter, as our body fat mass becomes obese, fat cells begin to function in a pro-inflammatory fashion and anti-inflammatory immune cells are replaced by pro-inflammatory immune cells. This can lead many to believe that their immune systems are anti-inflammatory if they are not overweight or obese, which is not necessarily true.

It is certainly possible for me to get 60% of my calories from refined sugar, flour, and omega-6 oils, and still keep my overall caloric intake at a level that does not cause me to gain weight. If I did this, I would still be deficient in key nutrients such as potassium, magnesium, iodine, omega-3 fatty acids, polyphenols, carotenoids, and simmering. I avoided sun exposure, I would also be deficient in vitamin D. If I were to do this, then my immune system would behave in a pro-inflammatory fashion that is similar to that which occurs in obese adipose tissue. Vitamin D deficiency provides us with the best example of this shift to a pro-inflammatory state.

Vitamin D deficiency and related supplementation has become extremely popular in the last 15-20 years. Research has identified that multiple diseases are promoted by a chronic deficiency of vitamin D. Table 1 below is from *The DeFlame Diet* book, which highlights many of the conditions related to a deficiency of vitamin D. Notice that the first four conditions on the left column demonstrate the importance of vitamin D for dealing with viruses and bacteria.

Table 1 - Potential consequences of vitamin D deficiency

Influenza	Muscle aches
Common cold	Schizophrenia
Tuberculosis	Depression
Bacterial vaginosis	Metabolic syndrome
Rickets	Type 1 diabetes
Osteoporosis (bone pain)	Osteoarthritis

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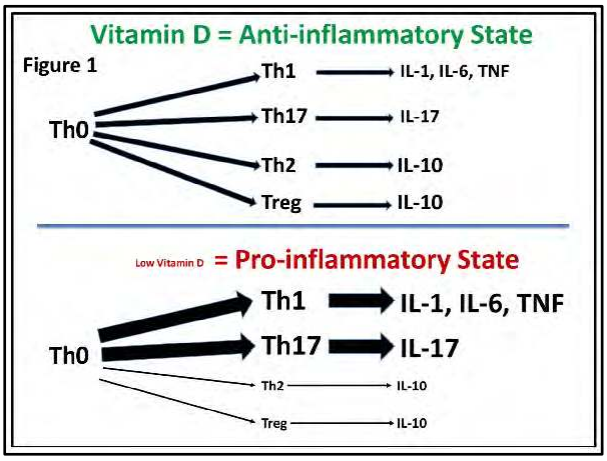

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Estimated needs of vit D throughout lifecycle

1. **Breast-fed infants (800 IU/day)**
2. **Formula-fed infants (400 IU/day)**
3. **Toddlers & young children (1000-2000 IU/day) – [when not getting adequate sun, and based on weight*]**
4. **Lactating women: 7,000 IU/day**
5. **Adolescents and adults can take between 3000-10000 IU or more depending on vitamin D levels in blood (serum 25(OH)D: 32-100 ng/ml).**
6. **Pregnant or those thinking of becoming pregnant – get 25(OH)D check every 3-months (*get to 40-70 ng/ml**)**

Read full text before acting: Cannell JJ, Hollis BW. Use of vitamin D(3) in clinical practice. Alt Med Rev. 2008;13(1):6-20.

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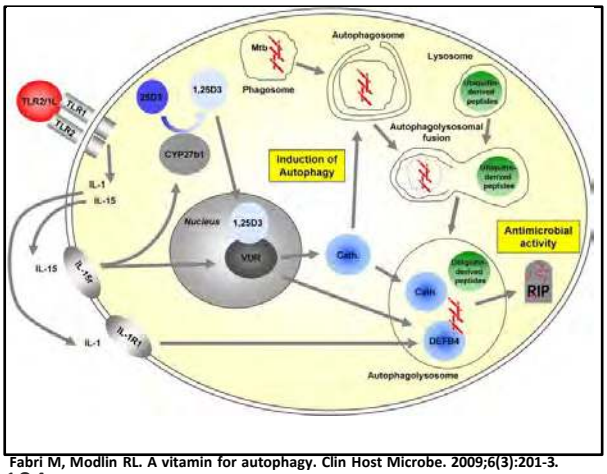

Fabri M, Modlin RL. A vitamin for autophagy. Clin Host Microbe. 2009;6(3):201-3.

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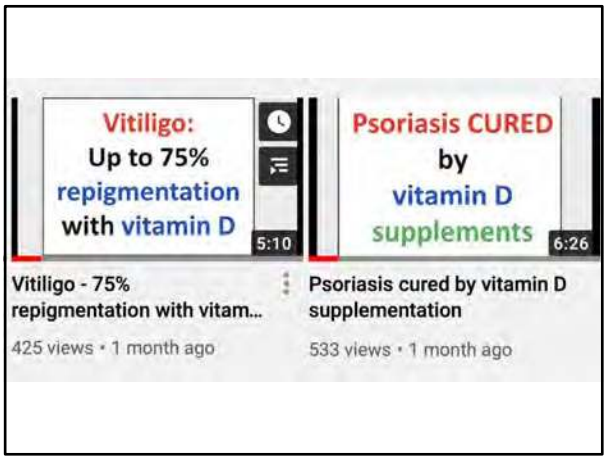

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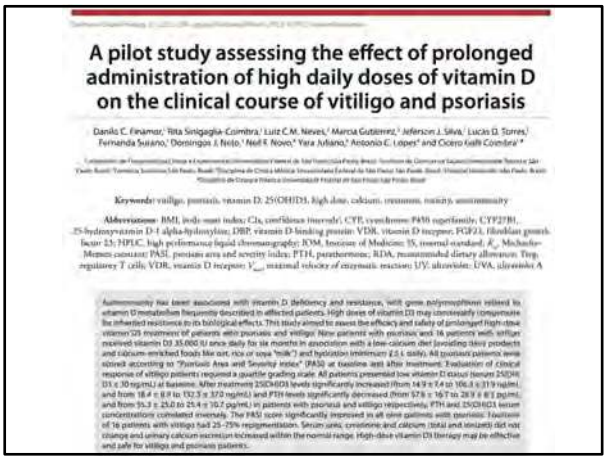

A pilot study assessing the effect of prolonged administration of high daily doses of vitamin D on the clinical course of vitiligo and psoriasis

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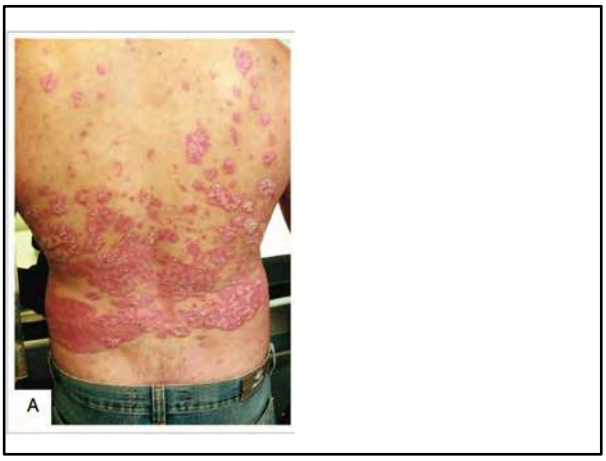

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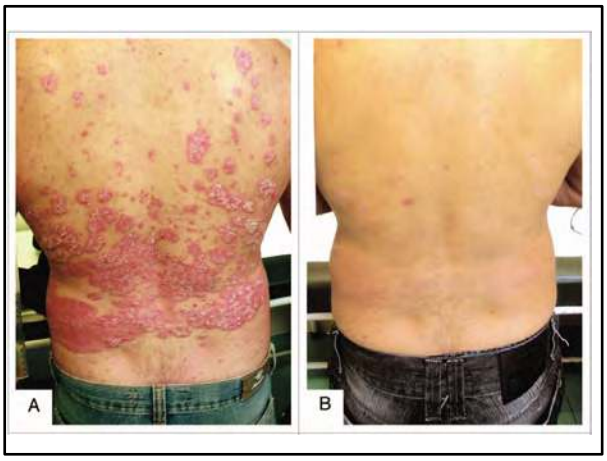

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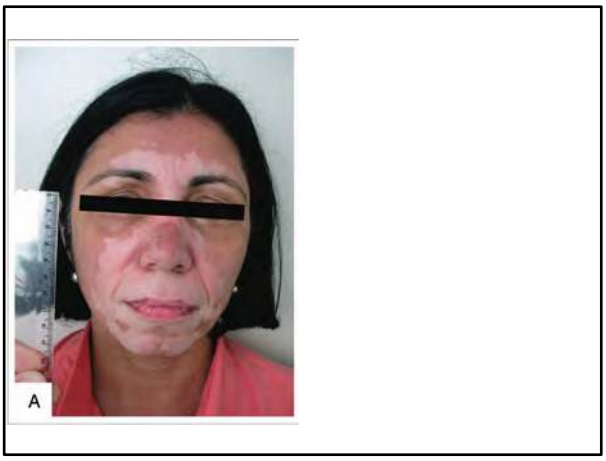

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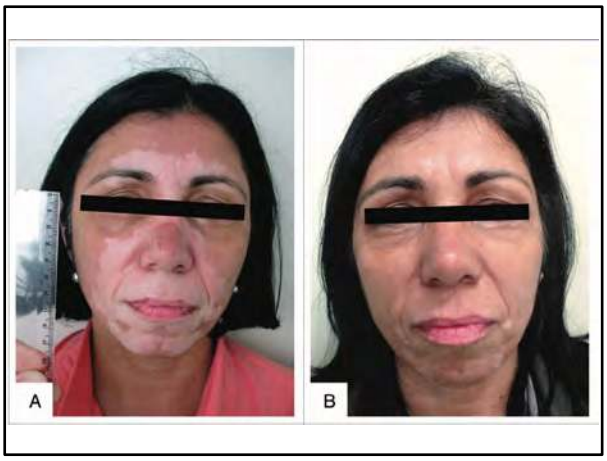

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Vitamin C supplementation reduces the incidence of postrace symptoms of upper-respiratory-tract infection in ultramarathon runners[1–3]

Edith M Peters, Jeanette M Goetzsche, Brian Grobbelaar, and Timothy D Noakes

ABSTRACT This study determined whether daily supplementation with 600 mg vitamin C would reduce the incidence of symptoms of upper-respiratory-tract (URT) infections after participation in a competitive ultramarathon race (> 42 km). Ultramarathon runners with age-matched controls were randomly divided into placebo and experimental (vitamin C–supplemented) groups. Symptoms of URT infections were monitored for 14 d after the race. Sixty-eight percent of the runners in the placebo group reported the development of symptoms of URT infection after the race; this was significantly more ($P < 0.01$) than that reported by the vitamin C–supplemented group (33%). The duration and severity of symptoms of URT infections reported in the vitamin C–supplemented nonrunning control group was also significantly less than in the nonrunning control group receiving the placebo ($P < 0.05$). This study provides evidence that vitamin C supplementation may enhance resistance to the postrace URT infections that occur commonly in competitive ultramarathon runners and may reduce the severity of such infections in those who are sedentary. *Am J Clin Nutr* 1993;57:170–4.

KEY WORDS Vitamin C, infection, ultramarathon running

Subjects and methods

Ninety-two runners who belonged to running clubs in the local area and who had entered the 1990 90-km Comrades Marathon, run annually between Durban and Pietermaritzburg, South Africa, volunteered to participate in this study. Each subject was required to nominate a control subject of similar age who was not a regular runner and who was prepared to supplement his or her vitamin C intake for the 21 d before the date the ultramarathon race was run. Consent was obtained from the runners and controls and the research protocol was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand Medical School.

A double-blind, placebo-controlled study was conducted: for the 21 d before the marathon, half the runners ($n = 46$) and half the control subjects ($n = 46$) were required to take one tablet containing 600 mg vitamin C daily, whereas the remaining runners ($n = 46$) and control subjects ($n = 46$) took an identical-looking and tasting placebo containing citric acid. Subjects were asked to complete questionnaires before the ultramarathon. These sought the following information: a brief training history with running distance per week, average running speed, number of weeks spent training, frequency of participation in other ul-

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Review

Vitamin C and Immune Function

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[2] Bayer Consumer Care Ltd., Peter-Merian-Strasse 84, 4002 Basel, Switzerland; silvia.maggini@bayer.com
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Abstract: Vitamin C is an essential micronutrient for humans, with pleiotropic functions related to its ability to donate electrons. It is a potent antioxidant and a cofactor for a family of biosynthetic and gene regulatory enzymes. Vitamin C contributes to immune defense by supporting various cellular functions of both the innate and adaptive immune system. Vitamin C supports epithelial barrier function against pathogens and promotes the oxidant scavenging activity of the skin, thereby potentially protecting against environmental oxidative stress. Vitamin C accumulates in phagocytic cells, such as neutrophils, and can enhance chemotaxis, phagocytosis, generation of reactive oxygen species, and ultimately microbial killing. It is also needed for apoptosis and clearance of the spent neutrophils from sites of infection by macrophages, thereby decreasing necrosis/NETosis and potential tissue damage. The role of vitamin C in lymphocytes is less clear, but it has been shown to enhance differentiation and proliferation of B- and T-cells, likely due to its gene regulating effects. Vitamin C deficiency results in impaired immunity and higher susceptibility to infections. In turn, infections significantly impact on vitamin C levels due to enhanced inflammation and metabolic requirements. Furthermore, supplementation with vitamin C appears to be able to both prevent and treat respiratory and systemic infections. Prophylactic prevention of infection requires dietary vitamin C intakes that provide at least adequate, if not saturating plasma levels (i.e., 100–200 mg/day), which optimize cell and tissue levels. In contrast, treatment of established infections requires significantly higher (gram) doses of the vitamin to compensate for the increased inflammatory response and metabolic demand.

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Review

Vitamin C and Immune Function

Table 1. Role of vitamin C in immune defense.

Immune System	Function of Vitamin C	Refs.
Epithelial barriers	Enhances collagen synthesis and stabilization	[30–35]
	Protects against ROS-induced damage [1]	[36–40]
	Enhances keratinocyte differentiation and lipid synthesis	[41–45]
	Enhances fibroblast proliferation and migration	[46,47]
	Shortens time to wound healing in patients	[48,49]
Phagocytes (neutrophils, macrophages)	Acts as an antioxidant/electron donor	[50–53]
	Enhances motility/chemotaxis	[54–63]
	Enhances phagocytosis and ROS generation	[64–71]
	Enhances microbial killing	[54,55,57,58,70,72]
	Facilitates apoptosis and clearance	[71,73,74]
	Decreases necrosis/NETosis	[73,75]
B- and T-lymphocytes	Enhances differentiation and proliferation	[62,63,76–82]
	Enhances antibody levels	[78,83–85]
Inflammatory mediators	Modulates cytokine production	[75,77,86–94]
	Decreases histamine levels	[56,61,95–101]

[1] ROS, reactive oxygen species; NET, neutrophil extracellular trap. Note that many of these studies comprised marginal or deficient vitamin C status at baseline. Supplementation in situations of adequate vitamin C status may not have comparable effects.

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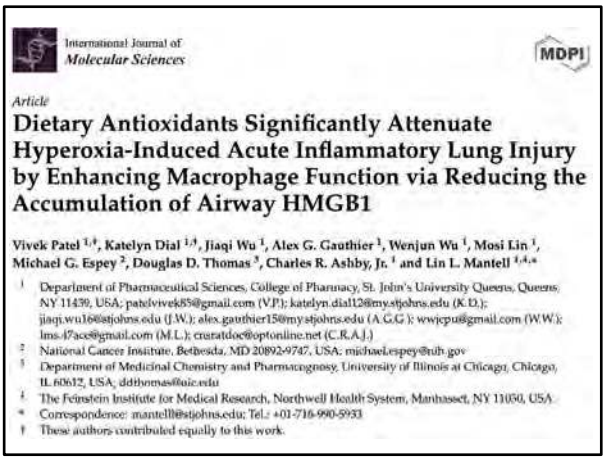

International Journal of *Molecular Sciences*

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Article

Dietary Antioxidants Significantly Attenuate Hyperoxia-Induced Acute Inflammatory Lung Injury by Enhancing Macrophage Function via Reducing the Accumulation of Airway HMGB1

Vivek Patel [1,†], Katelyn Dial [1,†], Jiaqi Wu [1], Alex G. Gauthier [1], Wenjun Wu [1], Mosi Lin [1], Michael G. Espey [2], Douglas D. Thomas [3], Charles R. Ashby, Jr. [4] and Lin L. Mantell [1,4,*]

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* Correspondence: mantell@stjohns.edu; Tel.: +01-718-990-5933
† These authors contributed equally to this work.

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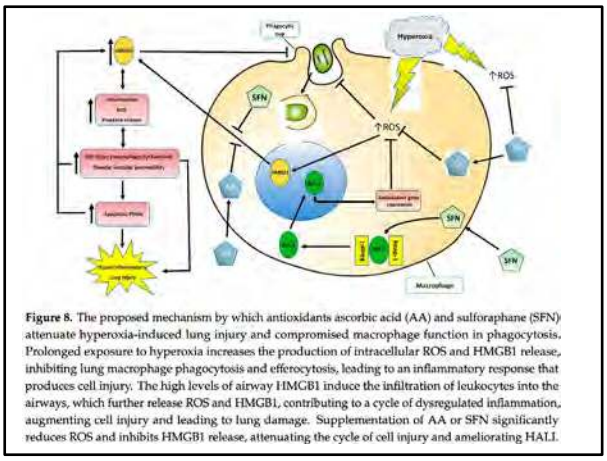

Figure 8. The proposed mechanism by which antioxidants ascorbic acid (AA) and sulforaphane (SFN) attenuate hyperoxia-induced lung injury and compromised macrophage function in phagocytosis. Prolonged exposure to hyperoxia increases the production of intracellular ROS and HMGB1 release, inhibiting lung macrophage phagocytosis and efferocytosis, leading to an inflammatory response that produces cell injury. The high levels of airway HMGB1 induce the infiltration of leukocytes into the airways, which further release ROS and HMGB1, contributing to a cycle of dysregulated inflammation, augmenting cell injury and leading to lung damage. Supplementation of AA or SFN significantly reduces ROS and inhibits HMGB1 release, attenuating the cycle of cell injury and ameliorating HALI.

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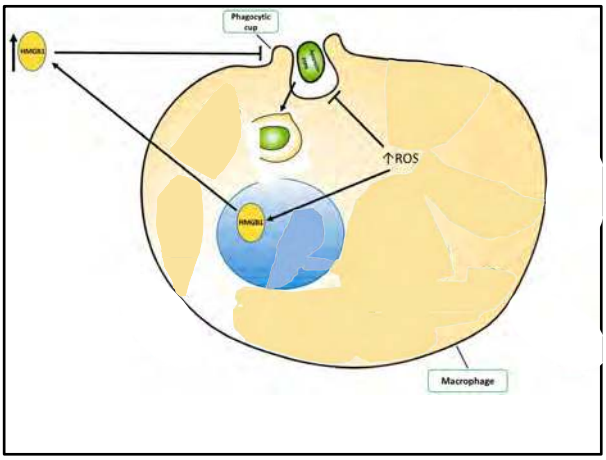

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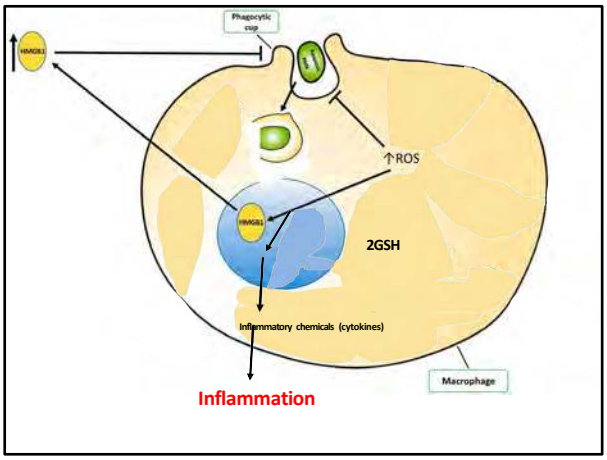

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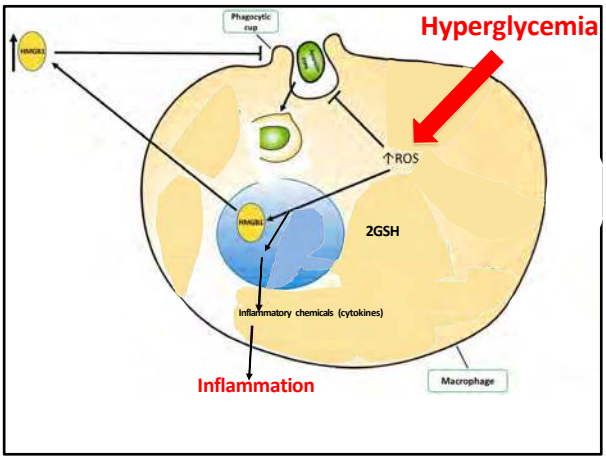

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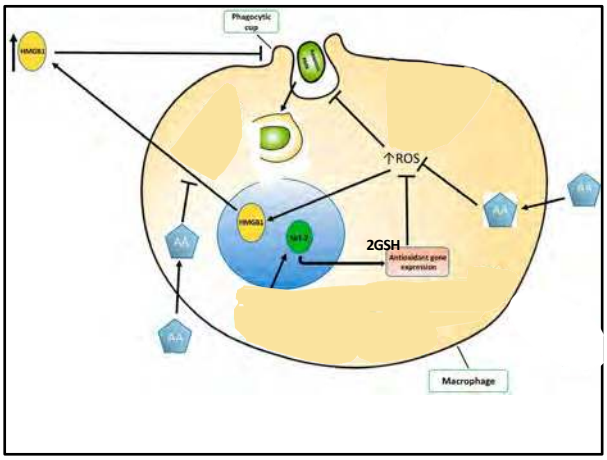

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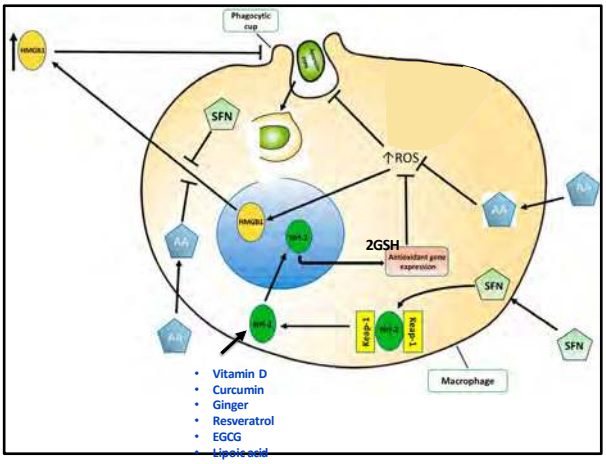

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Zinc supplementation decreases incidence of infections in the elderly: effect of zinc on generation of cytokines and oxidative stress[1–3]

Anandā S Prasad, Frances WJ Beck, Bin Bao, James T Fitzgerald, Diane C Snell, Joel D Steinberg, and Lavoisier J Cardozo

Design: A randomized, double-blind, placebo-controlled trial of zinc supplementation was conducted in elderly subjects. Fifty healthy subjects of both sexes aged 55–87 y and inclusive of all ethnic groups were recruited for this study from a senior center. The zinc-supplemented group received zinc gluconate (45 mg elemental Zn/d) orally for 12 mo. Incidence of infections during the supplementation period was documented. The generation of inflammatory cytokines, T helper 1 and T helper 2 cytokines, and oxidative stress markers and the plasma concentrations of zinc were measured at baseline and after supplementation.

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Zinc supplementation decreases incidence of infections in the elderly: effect of zinc on generation of cytokines and oxidative stress[1–3]

Anandā S Prasad, Frances WJ Beck, Bin Bao, James T Fitzgerald, Diane C Snell, Joel D Steinberg, and Lavoisier J Cardozo

Conclusions: After zinc supplementation, the incidence of infections was significantly lower, plasma zinc was significantly higher, and generation of tumor necrosis factor α and oxidative stress markers was significantly lower in the zinc-supplemented than in the placebo group. *Am J Clin Nutr* 2007;85:837–44.

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TABLE 3
Effect of zinc and placebo supplementation on clinical variables[1]

Variables	Subjects affected in 1 y: Zinc group (n = 24)	Subjects affected in 1 y: Placebo group (n = 25)	P^2
	%		
Infection	29	88	<0.001
Upper respiratory tract infection	12	24	0.136
Tonsillitis	0	8	0.255
Common cold	16	40	0.067
Cold sores	0	12	0.124
Flu	0	12	0.124
Fever	0	20	0.027
One infection each/y	29	52	
Two infections each/y	0	24	
Three infections each/y	0	8	
Four infections each/y	0	4	
Received antibiotics	8	48	

[1] Each subject could appear in >1 subcategory of infections.
[2] Chi-square Fisher's exact test.

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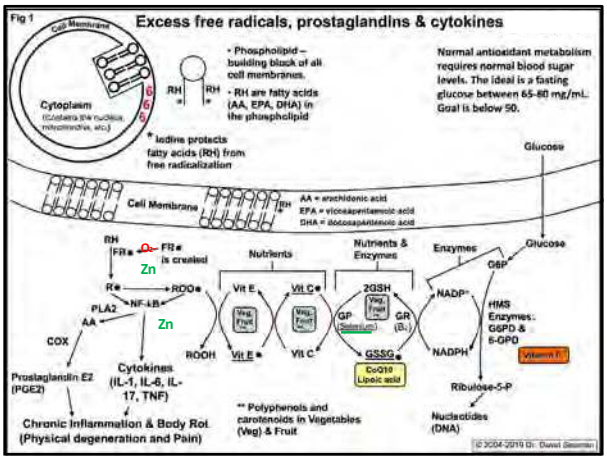

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REVIEW

WILEY

Curcumin (a constituent of turmeric): New treatment option against COVID-19

Fatemeh Babaei[1] | Marjan Nassiri-Asl[2] | Hossein Hosseinzadeh[3,4]

Abstract

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Goel A et al. Curcumin as "*curecumin*": from kitchen to clinic. Biochem Pharmacol. 2008;75:787-809.

- **Pilot phase I clinical trials have shown curcumin to be <u>safe</u> even when consumed at a daily dose of 12g for 3 months.**
- **Other clinical trials suggest a potential therapeutic role for curcumin in diseases:**

- **arthritis**
- **hypercholesteremia**
- **atherosclerosis**
- **pancreatitis**
- **psoriasis**
- **familial adenomatous polyposis**
- **inflammatory bowel disease**
- **chronic anterior uveitis**
- **ulcerative colitis**
- **colon cancer**
- **pancreatic cancer**

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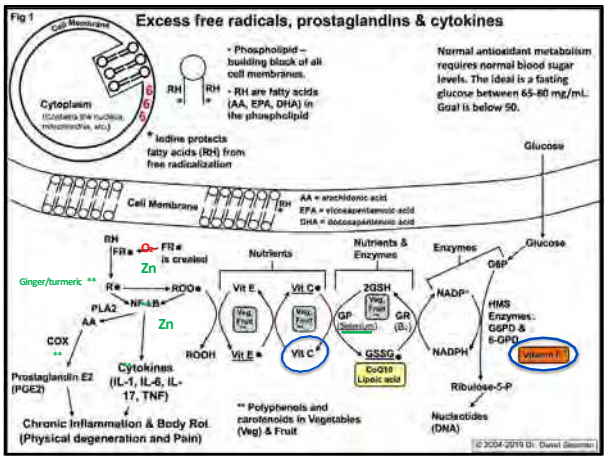

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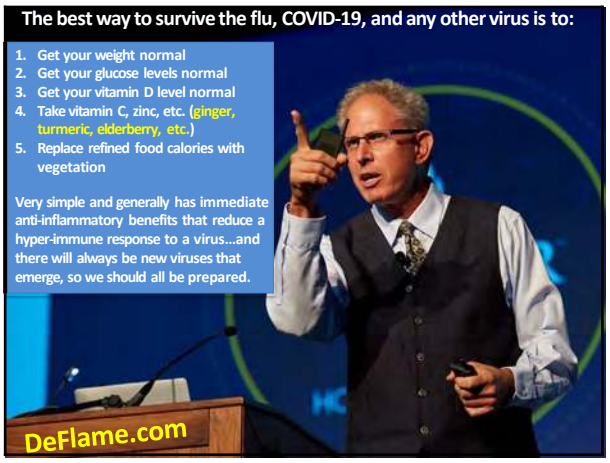

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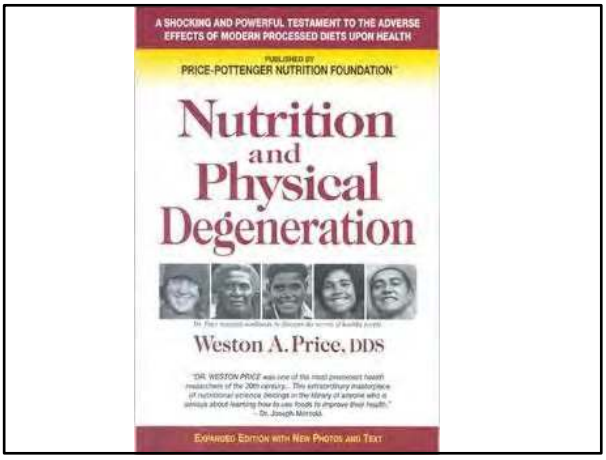

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NUTRITION AND PHYSICAL DEGENERATION

A Comparison of Primitive and Modern Diets and Their Effects

BY

WESTON A. PRICE, M.S., D.D.S., F.A.C.D.

Member Research Commission, American Dental Association
Member American Association of Physical Anthropologists
Honorary Member of the International Mark Twain Society
Honorary Fellowship in the International College of Dentists
Honorary Member of the American Academy of Applied Nutrition
Author "Dental Infections, Oral and Systemic"
"Dental Infections and the Degenerative Diseases"

[Printed first in 1945 or earlier]

FOREWORD BY
EARNEST ALBERT HOOTON, *Professor of Anthropology, Harvard University*

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Fig. 91. The excellence of skeletal development of the jungle Indians as expressed in the faces and dental arches, is illustrated in these views. Their fossils were selected from the animal life of the streams and the bush together with native plants.

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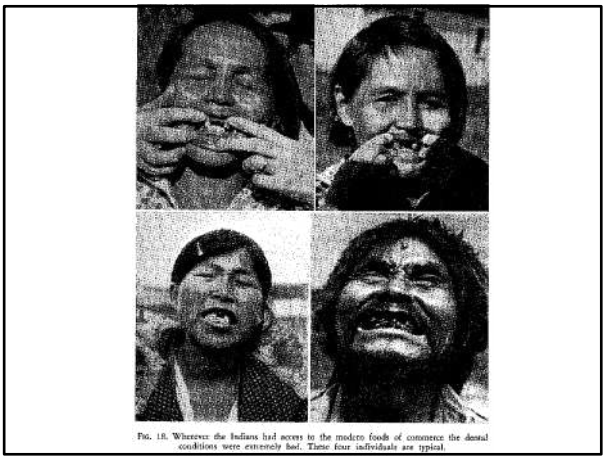

Fig. 18. Wherever the Indians had access to the modern foods of commerce the dental conditions were extremely bad. These four individuals are typical.

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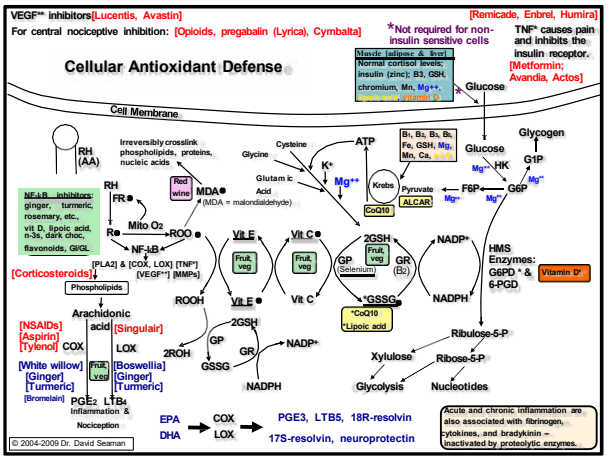

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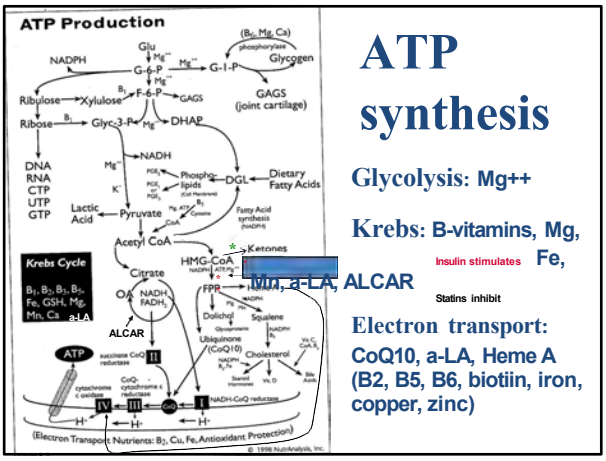

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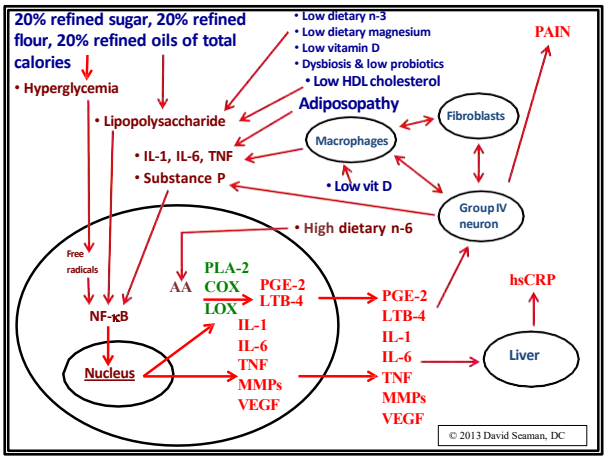

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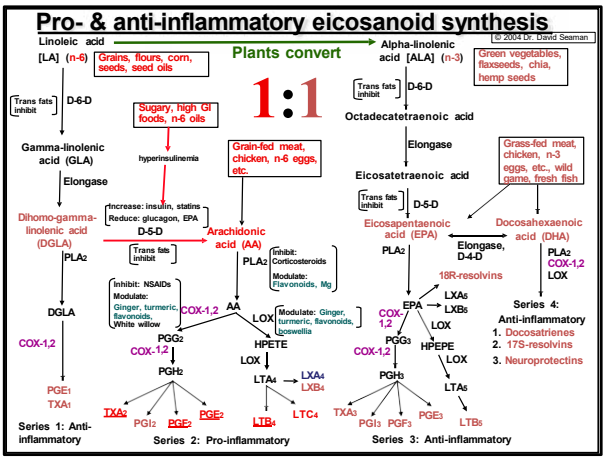

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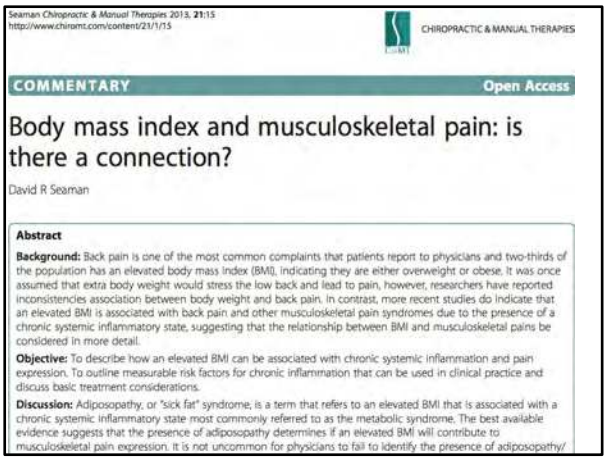

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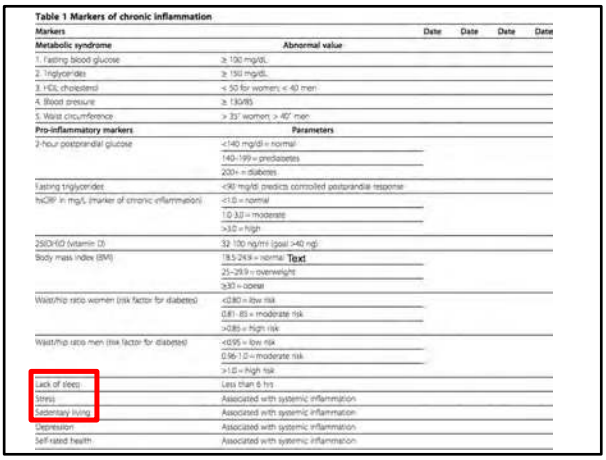

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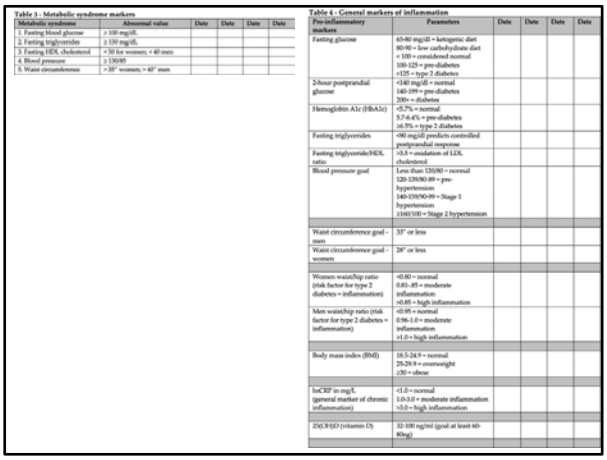

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The DeFlame Diet approach

1. Avoid excess calories…weigh what you weighed when you were in high-school or college

2. Avoid empty calories (refined sugar, flour, and oils) and excess salt

3. Maximize your nutrient/calorie ratio (example of whole grains vs vegetables)

4. Dietary options:
   - Vegan
   - Omnivore
   - Carnivore

5. Supplements:
   - Magnesium (mag)
   - Vitamin D (D)
   - Omega-3 (3)
   - Probiotics
   - Polyphenols (ginger/turmeric)
   - Iodine
   - Vitamin C
   - Zinc
   - CoQ10

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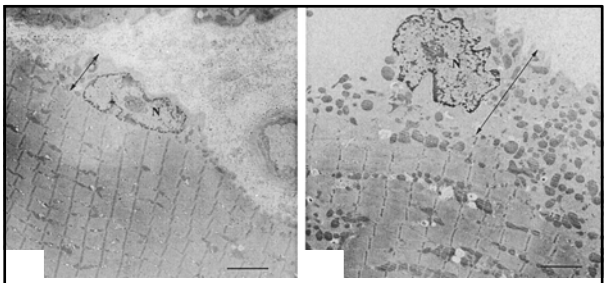

Electron micrograph of skeletal muscle.

Which one is normal??

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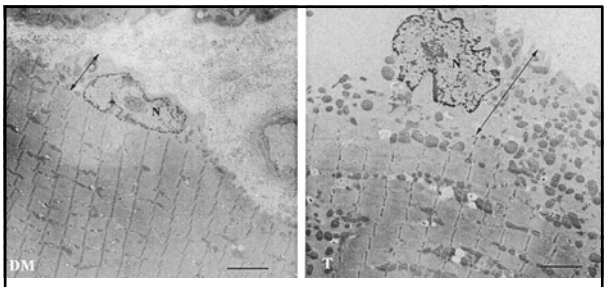

Representative transmission electron microscopy of longitudinal sections of human skeletal muscle from a lean (T) and a type 2 diabetic (DM) research volunteer are shown (bar = 2.5 µm). The thickness of the perinuclear distribution of subsarcolemmal mitochondria was measured using image analysis (National Institutes of Health image 1.61) and can be observed to be substantially depleted in type 2 diabetes.
Ritov VB et al. Deficiency of subsarcolemmal mitochondria in obesity and type 2 diabetes. Diabetes 2005; 54(1):8-14.

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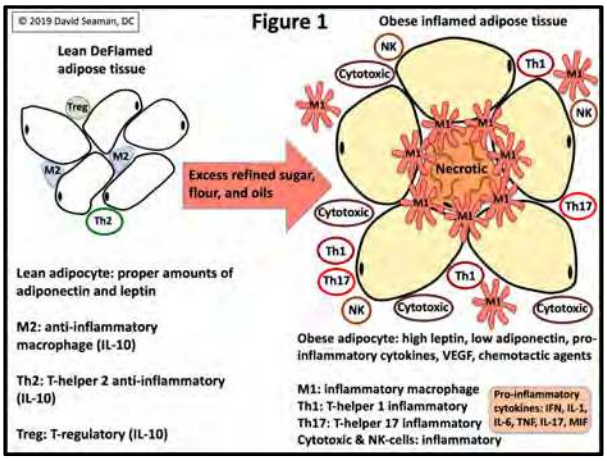

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HYPOTHESIS

Is progressive osteoarthritis an atheromatous vascular disease?

P G Conaghan, H Vanharanta, P A Dieppe

Ann Rheum Dis 2005;64:1539–1541. doi: 10.1136/ard.2005.039263

Growing evidence from epidemiological studies suggests that osteoarthritis (OA) is linked to atheromatous vascular disease. This hypothesis article proposes that OA, or at least OA structural progression, may be an atheromatous vascular disease of subchondral bone. Further epidemiological studies, imaging investigations of relevant blood vessels, and trials of the effects of statins on the prevention and treatment of OA are needed to examine this hypothesis.

Osteoarthritis (OA) is a massive problem for both individual patients and society. It is difficult to define, but there is a common clinical phenotype characterised by pain related to use and structural abnormalities of all tissues in the synovial joint, including cartilage, subchondral bone, synovium, capsule, and ligaments.[1] Vascular disease and OA are venous outflow obstruction[4] and hypercoagulability in both animal and human studies, described by Ghosh and Cheras.[5] The complexity of OA vascular abnormalities may be compounded by angiogenesis associated with inflammation in OA.[6]

Vascular disease in subchondral bone may accelerate the OA process either by altering cartilage nutrition[7] or through direct ischaemic effects on bone, if the subchondral bone is actually the first tissue affected and cartilage damage is secondary. Large segments of avascular bone necrosis, of the sort seen in association with steroid use, are relatively uncommon, but Bullough's group has demonstrated that multiple small bone infarcts are common in advanced OA.[8]

"Vascular disease in subchondral bone may accelerate the OA process"

Magnetic resonance imaging (MRI) can detect

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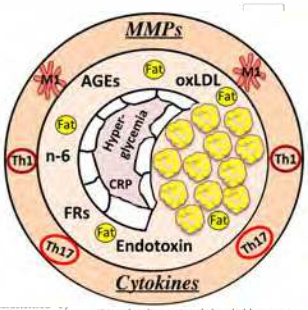
HYPOTHESIS

Is progressive osteoarthritis an atheromatous vascular disease?

P G Conaghan, H Vanharanta, P A Dieppe



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"Vascular disease in subchondral bone may accelerate the OA process"

Magnetic resonance imaging (MRI) can detect

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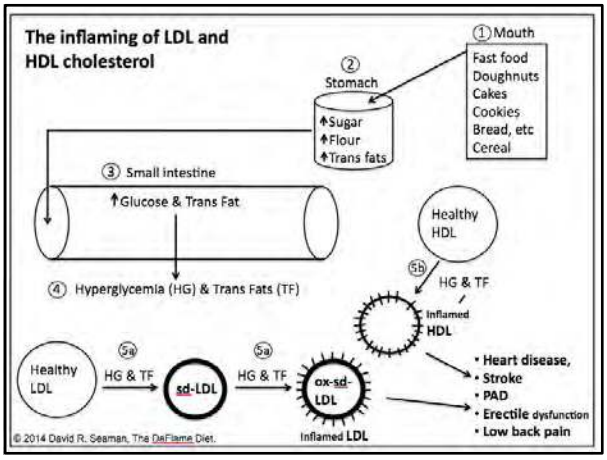

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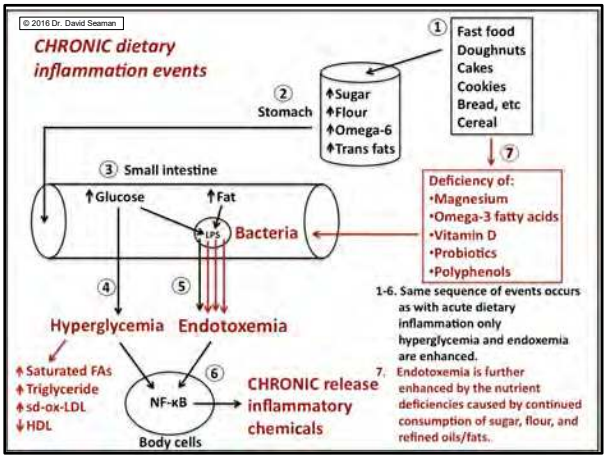

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Drivers of OA

(Salter RM. Continuous passive motion. Baltimore: Williams & Wilkins; 1993: p. 13)

- Congenital anomalies of joint: congenital dislocation of the hip, clubfeet
- Infections of joints: septic arthritis, tuberculosis arthritis
- Nonspecific inflammatory disorders: RA, AS
- Metabolic arthritis: gout, ochronosis
- Repeated hemarthrosis: hemophilia
- Injury: major trauma - intra-articular fractures, torn menisci
- Acquired incongruity of joint surfaces: avascular necrosis, slipped epiphysis
- Extra-articular deformities with malalignment of joints: genu varum, genu valgum
- Joint instability: lax ligaments, stretched capsule, subluxation
- Iatrogenic damage to art cartilage: compression necrosis

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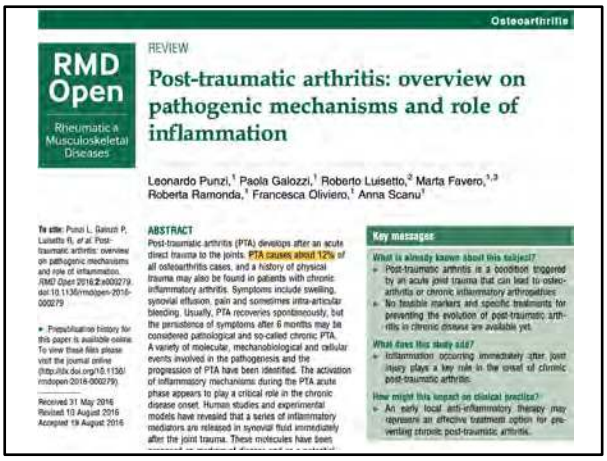

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Metabolic syndrome meets osteoarthritis

Qi Zhuo, Wei Yang, Jiying Chen and Yan Wang

Abstract | Metabolic osteoarthritis (OA) has now been characterized as a subtype of OA, and links have been discovered between this phenotype and metabolic syndrome (MetS)—both with individual MetS components and with MetS as a whole. Hypertension associates with OA through subchondral ischaemia, which can compromise nutrient exchange into articular cartilage and trigger bone remodelling. Ectopic lipid deposition in chondrocytes induced by dyslipidemia might initiate OA development, exacerbated by deregulated cellular lipid metabolism in joint tissues. Hyperglycaemia and OA interact at both local and systemic levels; local effects of oxidative stress and advanced glycation end-products are implicated in cartilage damage, whereas low-grade systemic inflammation results from glucose accumulation and contributes to a toxic internal environment that can exacerbate OA. Obesity-related metabolic factors, particularly altered levels of adipokines, contribute to OA development by inducing the expression of proinflammatory factors as well as degradative enzymes, leading to the inhibition of cartilage matrix synthesis and stimulation of subchondral bone remodelling. In this Review, we summarize the shared mechanisms of inflammation, oxidative stress, common metabolites and endothelial dysfunction that characterize the aetiologies of OA and MetS, and nominate metabolic OA as the fifth component of MetS. We also describe therapeutic opportunities that might arise from uniting these concepts.

Zhuo, Q. et al. Nat. Rev. Rheumatol. 8, 729–737 (2012); published online 21 August 2012; doi:10.1038/nrrheum.2012.135

Introduction

In 1986, the American College of Rheumatology defined osteoarthritis (OA) as "a heterogeneous group of conditions that lead to joint symptoms and signs, which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins".[1] OA is the most prevalent form of arthri-

MetS is prevalent in 59% of patients with OA and in 23% of the population without OA, in data from a sample of 7,714 people selected to represent the US population across all ages.[9] Studies have also found that people with MetS develop OA at an earlier age and have more generalised pathology, increased inflammation, and augmented inten-

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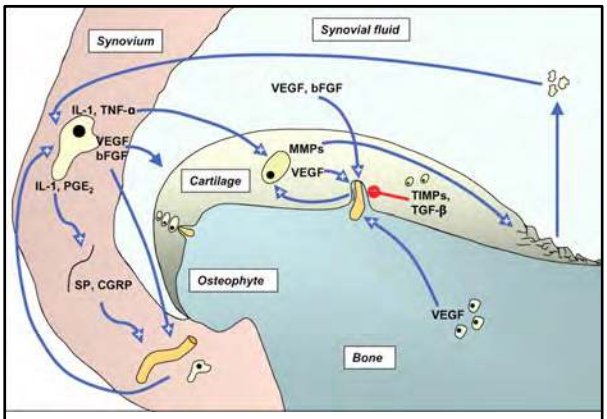

Bonnet CS, Walsh DA. Osteoarthritis, angiogenesis and inflammation. Rheumatology (Oxford). 2005 Jan;44(1):7-16

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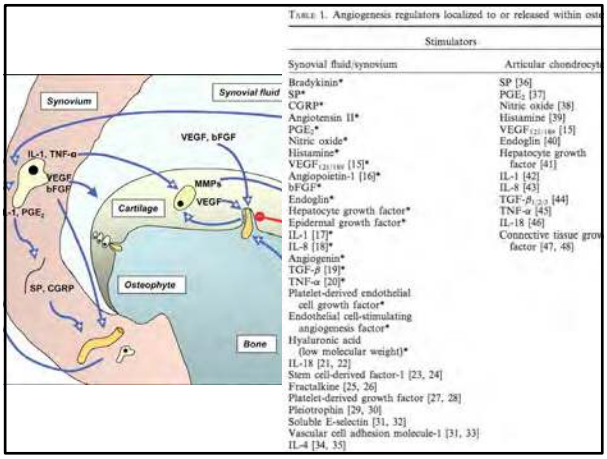

TABLE 1. Angiogenesis regulators localized to or released within oste

Stimulators	
Synovial fluid/synovium	Articular chondrocyt
Bradykinin*	SP [36]
SP*	PGE_2 [37]
CGRP*	Nitric oxide [38]
Angiotensin II*	Histamine [39]
PGE_2*	$VEGF_{121}$ [15]
Nitric oxide*	Endoglin [40]
Histamine*	Hepatocyte growth factor [41]
$VEGF_{121/189}$ [15]*	IL-1 [42]
Angiopoietin-1 [16]*	IL-8 [43]
bFGF*	$TGF-\beta_{1/2/3}$ [44]
Endoglin*	TNF-α [45]
Hepatocyte growth factor*	IL-18 [46]
Epidermal growth factor*	Connective tissue grow factor [47, 48]
IL-1 [17]*	
IL-8 [18]*	
Angiogenin*	
$TGF-\beta$ [19]*	
TNF-α [20]*	
Platelet-derived endothelial cell growth factor*	
Endothelial cell-stimulating angiogenesis factor*	
Hyaluronic acid (low molecular weight)*	
IL-18 [21, 22]	
Stem cell-derived factor-1 [23, 24]	
Fractalkine [25, 26]	
Platelet-derived growth factor [27, 28]	
Pleiotrophin [29, 30]	
Soluble E-selectin [31, 32]	
Vascular cell adhesion molecule-1 [31, 33]	
IL-8 [34, 35]	

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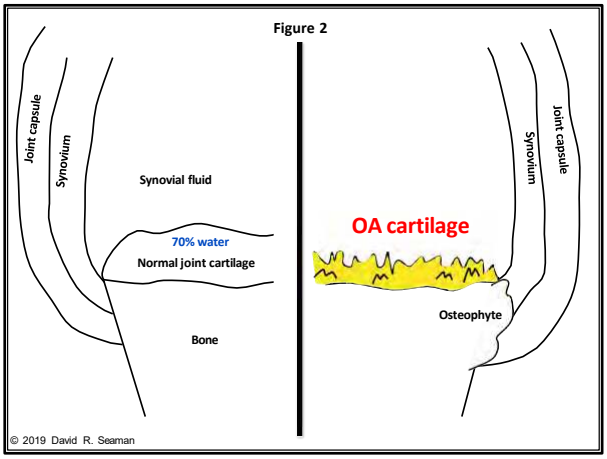

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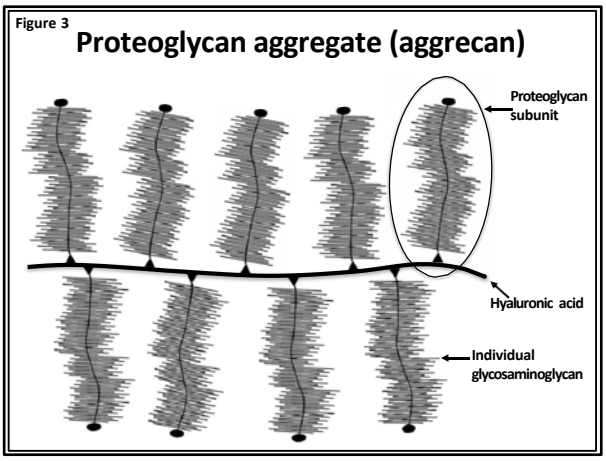

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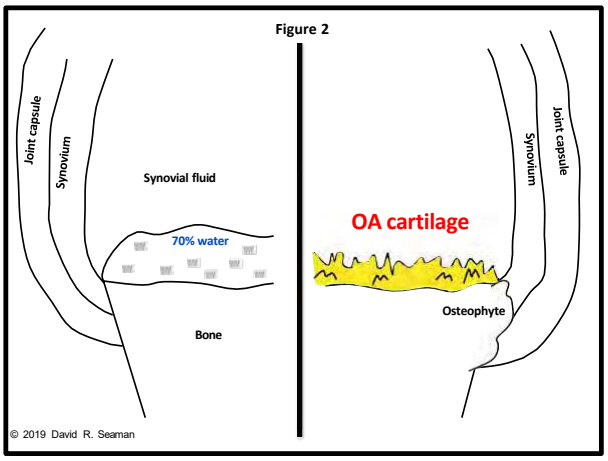

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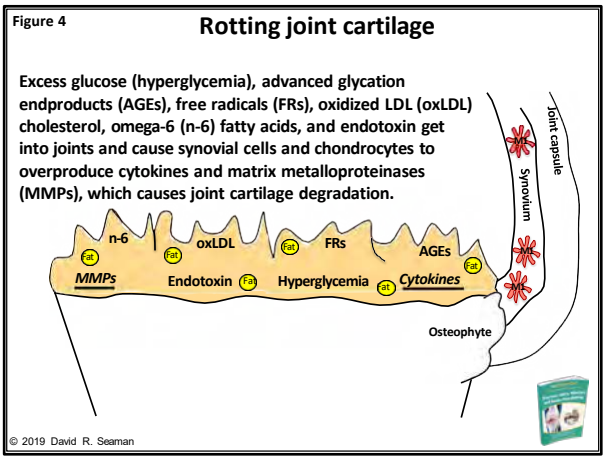

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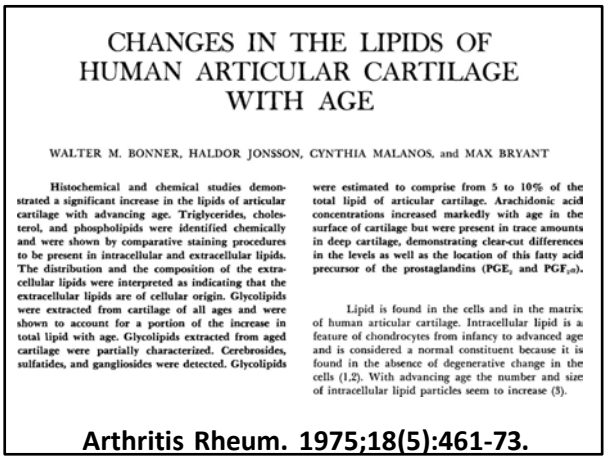

CHANGES IN THE LIPIDS OF HUMAN ARTICULAR CARTILAGE WITH AGE

WALTER M. BONNER, HALDOR JONSSON, CYNTHIA MALANOS, and MAX BRYANT

Histochemical and chemical studies demonstrated a significant increase in the lipids of articular cartilage with advancing age. Triglycerides, cholesterol, and phospholipids were identified chemically and were shown by comparative staining procedures to be present in intracellular and extracellular lipids. The distribution and the composition of the extracellular lipids were interpreted as indicating that the extracellular lipids are of cellular origin. Glycolipids were extracted from cartilage of all ages and were shown to account for a portion of the increase in total lipid with age. Glycolipids extracted from aged cartilage were partially characterized. Cerebrosides, sulfatides, and gangliosides were detected. Glycolipids were estimated to comprise from 5 to 10% of the total lipid of articular cartilage. Arachidonic acid concentrations increased markedly with age in the surface of cartilage but were present in trace amounts in deep cartilage, demonstrating clear-cut differences in the levels as well as the location of this fatty acid precursor of the prostaglandins (PGE_2 and $PGF_{2\alpha}$).

Lipid is found in the cells and in the matrix of human articular cartilage. Intracellular lipid is a feature of chondrocytes from infancy to advanced age and is considered a normal constituent because it is found in the absence of degenerative change in the cells (1,2). With advancing age the number and size of intracellular lipid particles seem to increase (3).

Arthritis Rheum. 1975;18(5):461-73.

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Normal Cartilage: no n-6 fatty acids

Normal, young cartilages, in distinction from all other tissues examined, have unusually high levels of n-9 (20:3) PUFA (Mead acid) and low levels of n-6 PUFA.

This apparent deficiency is consistently observed in cartilage of all species so far studied (young chicken,fetal calf,new born pig, rabbit, and human), even though levels of n-6 PUFA in blood and all other tissues is normal.

Because eicosanoids, which are derived from EFA, have been implicated in the inflammatory responses associated with arthritic disease, reduction of n-6 PUFA and accumulation of the n-9 20:3 acid in cartilage may be important for maintaining normal cartilage structure.

Adkisson HD et al. Unique fatty acid composition of normal cartilage: discovery of high levels of n-9 eicosatrienoic acid and low levels of n-6 polyunsaturated fatty acids. FASEB J. 1991; 5(3):344-53.

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Review

Lipid metabolism and osteoarthritis: Lessons from atherosclerosis

Vasiliki Gkretsi [a], Theodora Simopoulou [b], Aspasia Tsezou [a,b,c,*]

ARTICLE INFO

ABSTRACT

Osteoarthritis (OA) is an age-related degenerative disease comprising the main reason of handicap in the Western world. Interestingly, to date, there are neither available biomarkers for early diagnosis of the disease nor any effective therapy other than symptomatic treatment and joint replacement surgery. OA has long been associated with obesity, mainly due to mechanical overload exerted on the joints. Recent studies however, point to the direction that OA is a metabolic disease, as it also involves non-weight bearing joints. In fact, altered lipid metabolism may be the underlying cause. First, adipokines have been shown to be key regulators of OA pathogenesis. Second, epidemiological studies have shown serum cholesterol to be a risk factor for OA development. Third, lipid deposition in the joint is observed in the early stages of OA before the occurrence of histological changes. Fourth, proteomic analyses have shown an important connection between OA and lipid metabolism. Finally, recent gene expression studies reveal a deregulation of cholesterol influx and efflux and in the expression of lipid metabolism related genes. Interestingly, lipids and lipid metabolism are known to be implicated in the development and progression of another age-related degenerative disease, atherosclerosis (ATH). Thus, although it is tempting to speculate that the osteoarthritic chondrocyte has been transformed to foam cell, it has not been proven yet. However, this may be an intriguing theory linking ATH and OA, which may open new avenues to novel therapeutic interventions for OA taking advantage of previous knowledge from ATH.

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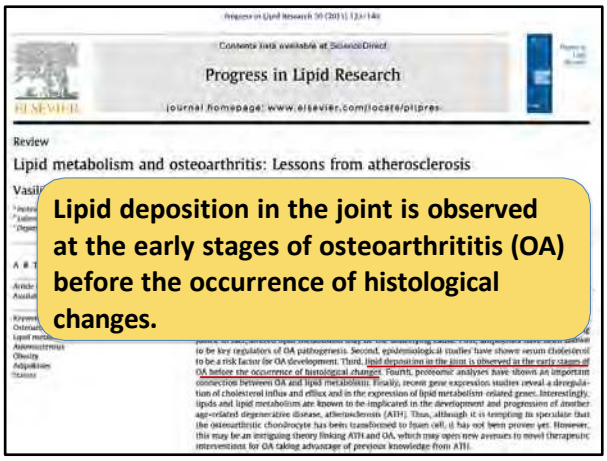

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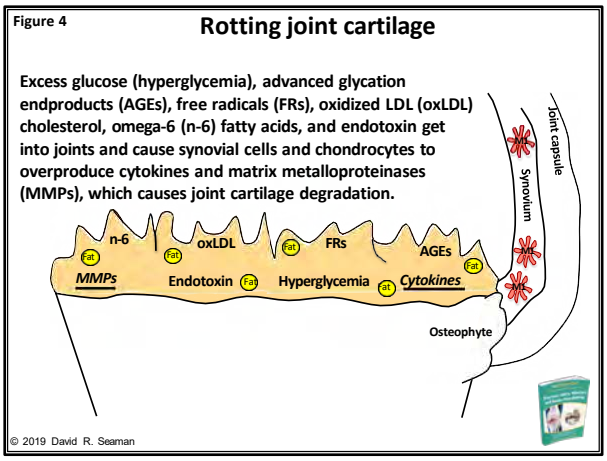

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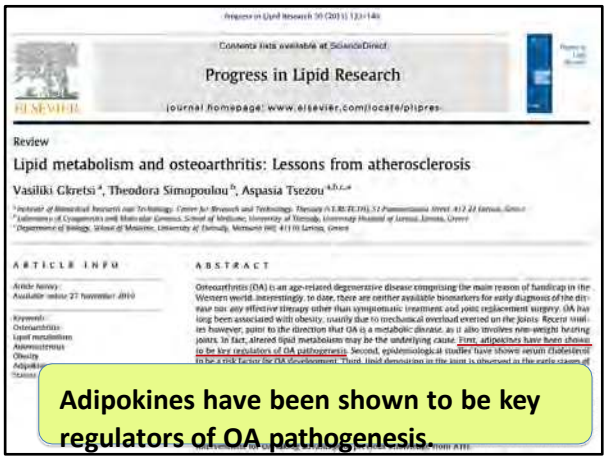

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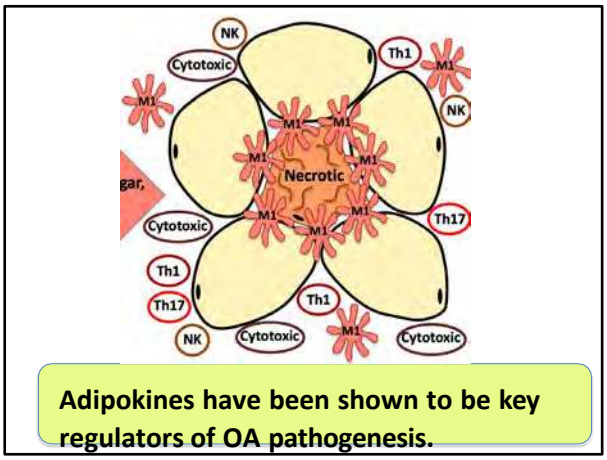

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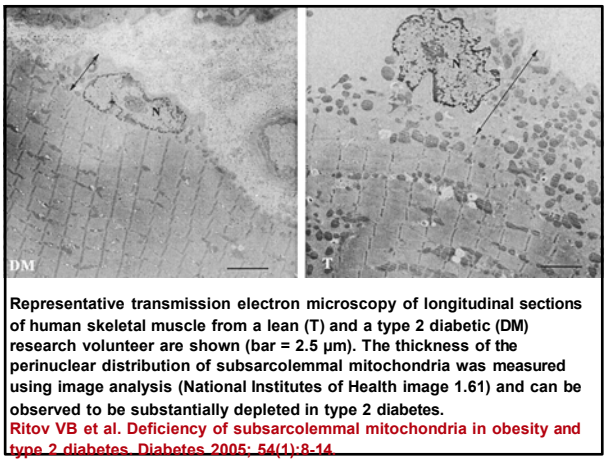

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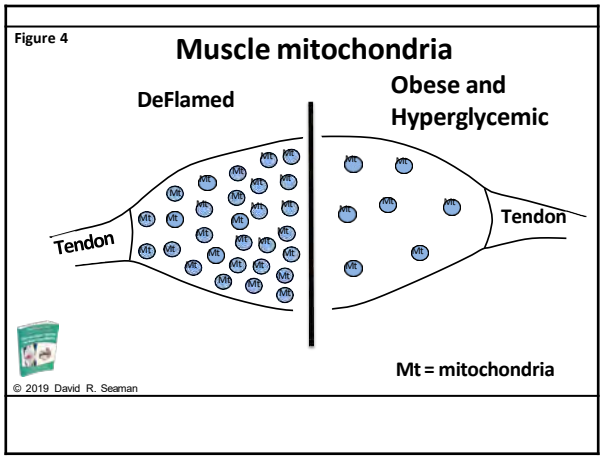

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Role of adiponectin in human skeletal muscle bioenergetics

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Summary

Insulin resistance is associated with impaired skeletal muscle oxidation capacity and reduced mitochondrial number and function. Here, we report that adiponectin signaling regulates mitochondrial bioenergetics in skeletal muscle. Individuals with a family history of type 2 diabetes display skeletal muscle insulin resistance and mitochondrial dysfunction; adiponectin levels strongly correlate with mtDNA content. Knockout of the adiponectin gene in mice is associated with insulin resistance and low mitochondrial content and reduced mitochondrial enzyme activity in skeletal muscle. Adiponectin treatment of human myotubes in primary culture induces mitochondrial biogenesis, palmitate oxidation, and citrate synthase activity, and reduces the production of reactive oxygen species. The inhibition of adiponectin receptor expression by siRNA, or of AMPK by a pharmacological agent, blunts adiponectin induction of mitochondrial function. Our findings define a skeletal muscle pathway by which adiponectin increases mitochondrial number and function and exerts antidiabetic effects.

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Figure 4

Muscle mitochondria = Mt

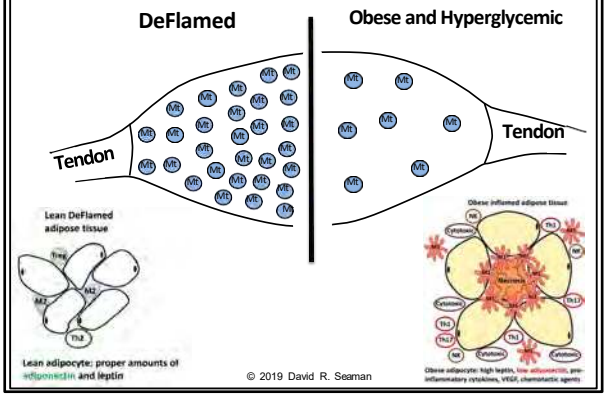

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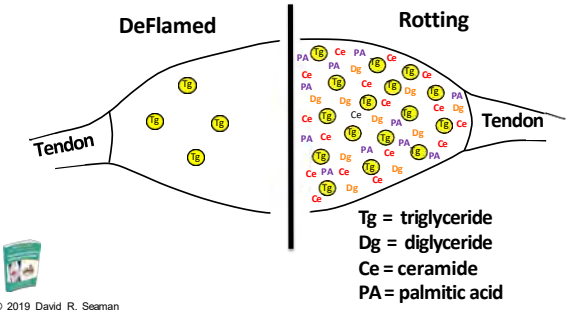
Figure 3

Muscle lipids



Tg = triglyceride
Dg = diglyceride
Ce = ceramide
PA = palmitic acid

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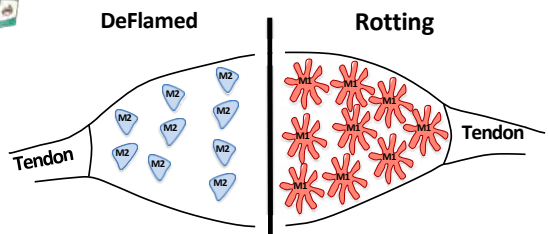
Figure 5

Muscle macrophages



M2 = anti-inflammatory macrophage

M1 = pro-inflammatory macrophage

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Figure 6

Muscle cells

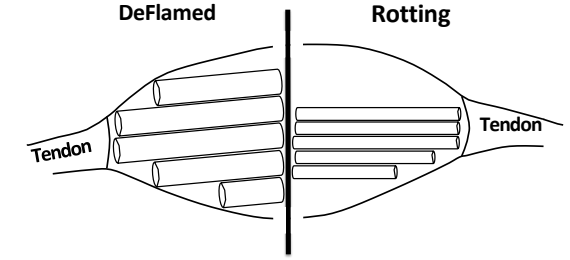

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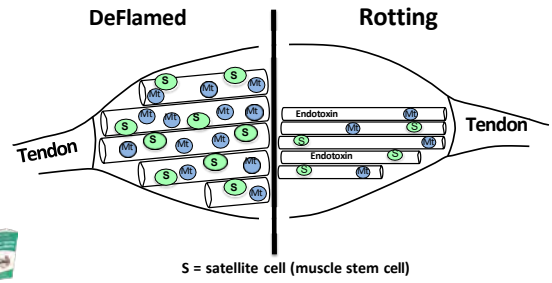
Figure 7

Muscle regenerative and energy producing capacity



S = satellite cell (muscle stem cell)
Mt = mitochondria

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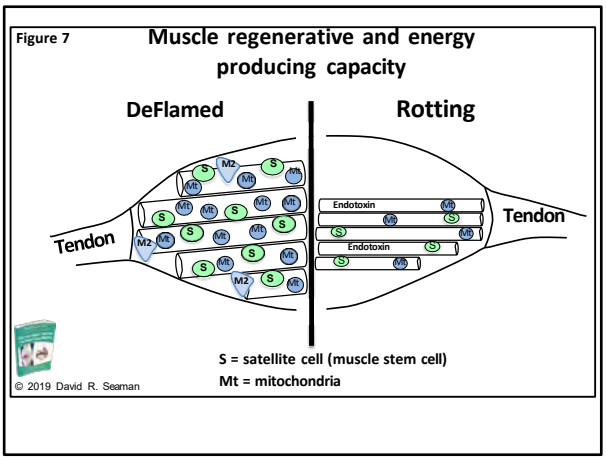

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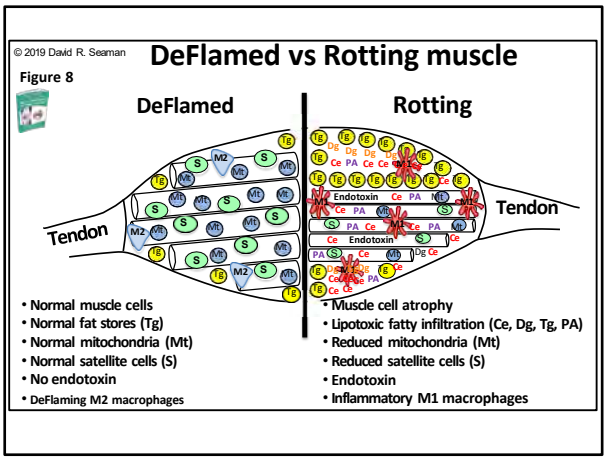

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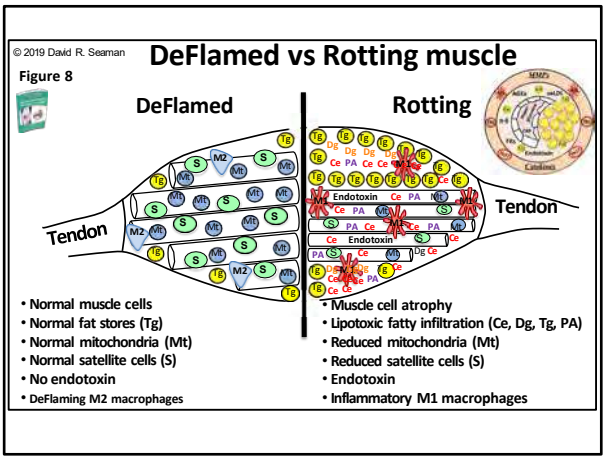

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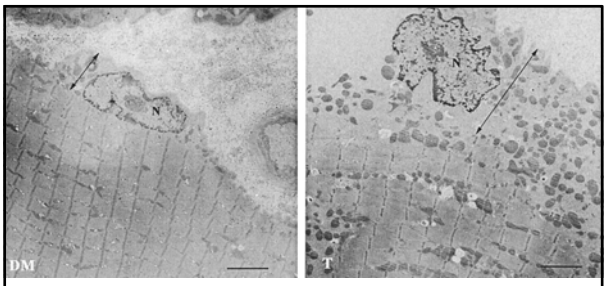

Representative transmission electron microscopy of longitudinal sections of human skeletal muscle from a lean (T) and a type 2 diabetic (DM) research volunteer are shown (bar = 2.5 μm). The thickness of the perinuclear distribution of subsarcolemmal mitochondria was measured using image analysis (National Institutes of Health image 1.61) and can be observed to be substantially depleted in type 2 diabetes.
Ritov VB et al. Deficiency of subsarcolemmal mitochondria in obesity and type 2 diabetes. Diabetes 2005; 54(1):8-14.

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CLINICAL SCIENCES

Dyslipidemia in Achilles Tendinopathy Is Characteristic of Insulin Resistance

JAMES EDMUND GAIDA[1], LOTTA ALFREDSON[2], ZOLTAN STEVEN KISS[2], ANDREW MICHAEL WILSON[5], HÅKAN ALFREDSON[2], and JILL LEIGH COOK[5]

If tendinopathy is confirmed to be associated with dyslipidemia and the metabolic syndrome in larger studies, it may be appropriate to redefine our concept of tendinopathy to that of a cardiovascular disease (CVD).

In this case, we may be able to draw considerably on CVD research to improve our understanding of tendinopathy, and perhaps treating CVD risk factors will improve the treatment of tendinopathy.

Key Words: ACHILLES TENDON, MIDPORTION, SERUM, LIPID

Med Sci Sports Exerc 2009;41:1194-1197.

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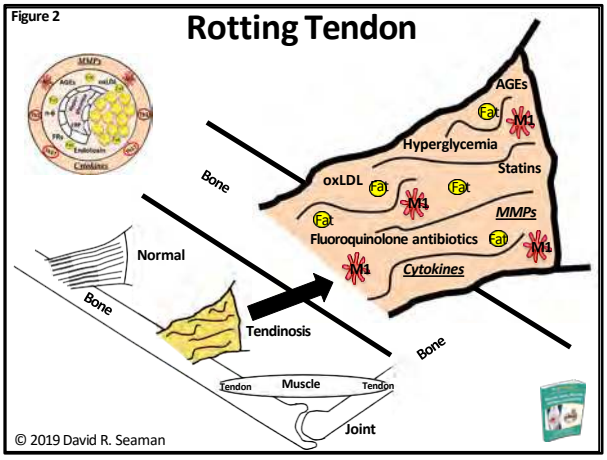

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RESEARCH ARTICLE Open Access

Asymptomatic Achilles tendon pathology is associated with a central fat distribution in men and a peripheral fat distribution in women: a cross sectional study of 298 individuals

James E Gaida[1*], Håkan Alfredson[2], Zoltan S Kiss[3], Shona L Bass[1], Jill L Cook[1]

BMC Musculoskelet Disord 2010, 11:41.

Abstract

Background: Adiposity is a modifiable factor that has been implicated in tendinopathy. As tendon pain reduces physical activity levels and can lead to weight gain, associations between tendon pathology and adiposity must be studied in individuals without tendon pain. Therefore, the purpose of this study was to determine whether fat distribution was associated with asymptomatic Achilles tendon pathology.

Methods: The Achilles tendons of 298 individuals were categorised as normal or pathological using diagnostic ultrasound. Fat distribution was determined using anthropometry (waist circumference, waist hip ratio [WHR]) and dual-energy x-ray absorptiometry.

Results: Asymptomatic Achilles tendon pathology was more evident in men (139) than women (59) ($p = 0.007$). Men with tendon pathology were older (50.9 ± 10.4, 36.3 ± 11.3, $p < 0.001$), had greater WHR (0.926 ± 0.091, 0.875 ± 0.065, $p = 0.039$), higher android/gynoid fat mass ratio (0.616 ± 0.186, 0.519 ± 0.142, $p = 0.014$) and higher upper-body/lower body fat mass ratio (2.346 ± 0.630, 2.022 ± 0.467, $p = 0.013$). Men older than 40 years with a waist circumference >88 cm had the greatest prevalence of tendon pathology (33%). Women with tendon pathology were older (47.4 ± 10.0,

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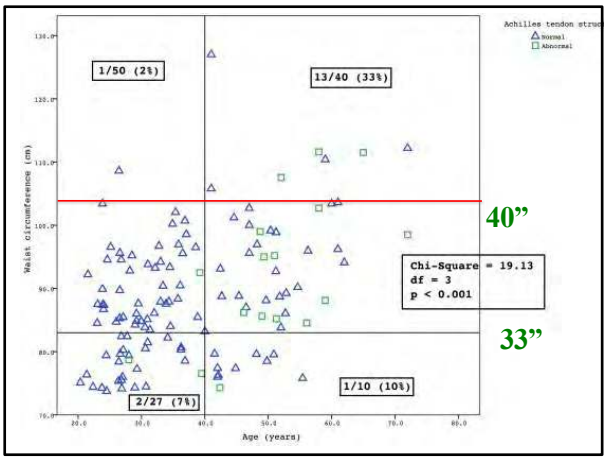

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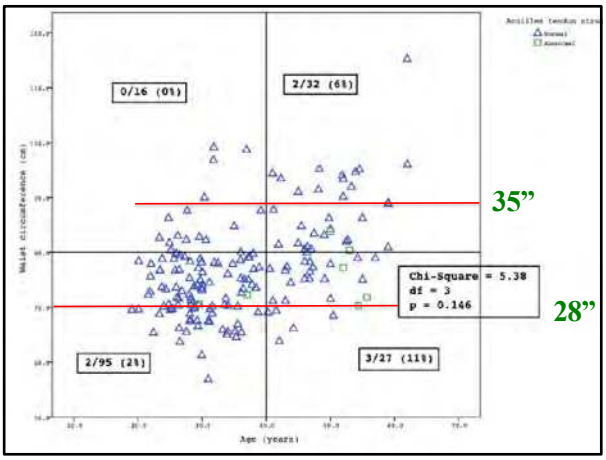

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Seaman Chiropractic & Manual Therapies 2013, 21:15
http://www.chiromt.com/content/21/1/15

CHIROPRACTIC & MANUAL THERAPIES

COMMENTARY Open Access

Body mass index and musculoskeletal pain: is there a connection?

David R Seaman

Abstract

Background: Back pain is one of the most common complaints that patients report to physicians and two-thirds of the population has an elevated body mass index (BMI), indicating they are either overweight or obese. It was once assumed that extra body weight would stress the low back and lead to pain, however, researchers have reported inconsistencies association between body weight and back pain. In contrast, more recent studies do indicate that an elevated BMI is associated with back pain and other musculoskeletal pain syndromes due to the presence of a chronic systemic inflammatory state, suggesting that the relationship between BMI and musculoskeletal pains be considered in more detail.

Objective: To describe how an elevated BMI can be associated with chronic systemic inflammation and pain expression. To outline measurable risk factors for chronic inflammation that can be used in clinical practice and discuss basic treatment considerations.

Discussion: Adiposopathy, or "sick fat" syndrome, is a term that refers to an elevated BMI that is associated with a chronic systemic inflammatory state most commonly referred to as the metabolic syndrome. The best available evidence suggests that the presence of adiposopathy determines if an elevated BMI will contribute to musculoskeletal pain expression. It is not uncommon for physicians to fail to identify the presence of adiposopathy/

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Table 1 Markers of chronic inflammation

Markers		Date	Date	Date	Date
Metabolic syndrome	**Abnormal value**				
1. Fasting blood glucose	≥ 100 mg/dL				
2. Triglycerides	≥ 150 mg/dL				
3. HDL cholesterol	< 50 for women; < 40 men				
4. Blood pressure	≥ 130/85				
5. Waist circumference	> 35" women; > 40" men				
Pro-inflammatory markers	**Parameters**				
2-hour postprandial glucose	<140 mg/dl = normal 140–199 = prediabetes 200+ = diabetes				
Fasting triglycerides	<90 mg/dl predicts controlled postprandial response				
hsCRP in mg/L (marker of chronic inflammation)	<1.0 = normal 1.0-3.0 = moderate >3.0 = high				
25(OH)D (vitamin D)	32-100 ng/ml (goal >40 ng)				
Body mass index (BMI)	18.5-24.9 = normal; Text 25–29.9 = overweight ≥30 = obese				
Waist/hip ratio women (risk factor for diabetes)	<0.80 = low risk 0.81-.85 = moderate risk >0.85 = high risk				
Waist/hip ratio men (risk factor for diabetes)	<0.95 = low risk 0.96-1.0 = moderate risk >1.0 = high risk				
Lack of sleep	Less than 6 hrs				
Stress	Associated with systemic inflammation				
Sedentary living	Associated with systemic inflammation				
Depression	Associated with systemic inflammation				
Self-rated health	Associated with systemic inflammation				

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The DeFlame Diet approach

1. Avoid excess calories…weigh what you weighed when you were in high-school or college and maintain normal levels of inflammatory markers

2. Avoid empty calories (refined sugar, flour, and oils) and excess salt

3. Maximize your nutrient/calorie ratio (example of whole grains vs vegetables)

4. Dietary options:

Vegan

Omnivore

Carnivore

5. Supplements:

- **Multivitamin/mineral**
- **Magnesium (mag)**
- **Vitamin D (D)**
- **Omega-3 (3)**
- **Probiotics**
- **Polyphenols (ginger/turmeric, etc.)**
- **Iodine (contraindicated in Hashimoto's disease)**
- **Vitamin C**
- **Zinc**
- **CoQ10**
- **Glucosamine/chondroitin**

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