Casual Friday Series

Heavy-Hitting Heavy Metals II
Lead

A BIOGENETIX CLINICAL PRESENTATION
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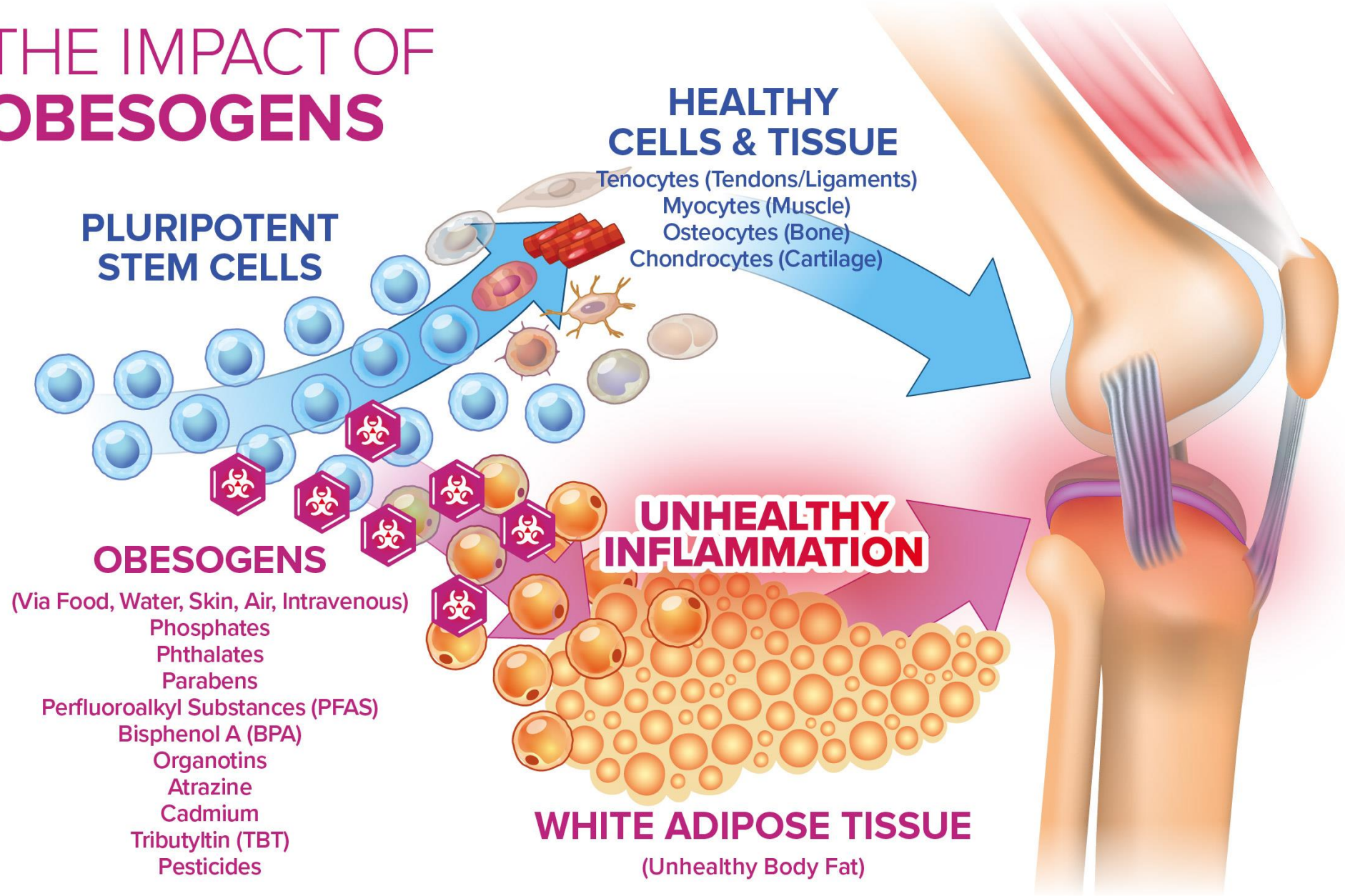
THE IMPACT OF **OBESOGENS**



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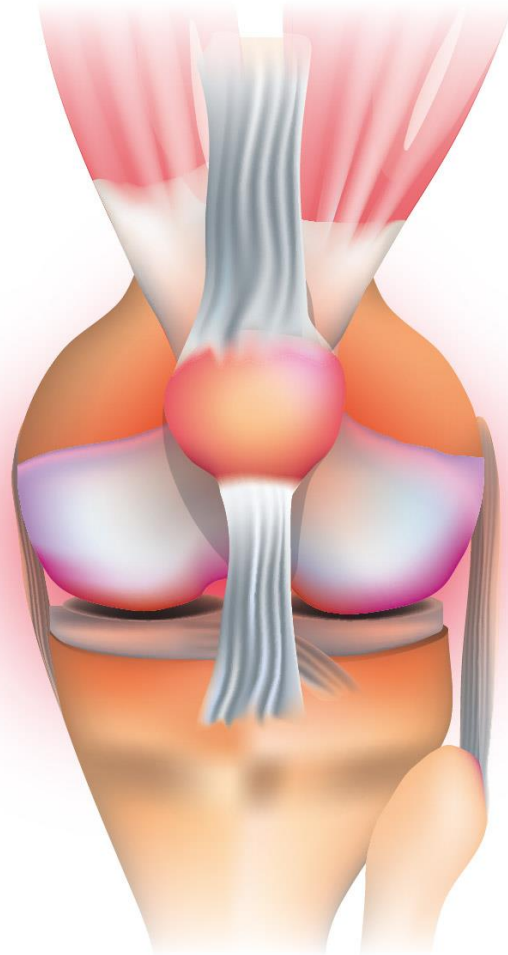
THE **ADIPOKINE** SPIRAL



1
Obesogens Drive
Stem Cells into Adipocytes

2
Adiposity Increases

3
Increased
Adipokine Activity

4
Triggering
Increased
Unhealthy Inflammation

5
Ongoing
Tissue Damage

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Adipokines

Adipokines are proteins produced by adipose tissue that can be pro- or anti-inflammatory. Some examples of adipokines include:

- **Leptin**: A pro-inflammatory adipokine that comes from adipocytes
- **Resistin**: A pro-inflammatory adipokine that comes from adipocytes and peripheral blood mononuclear cells
- **Adiponectin**: An adipokine that can be anti-inflammatory
- **Visfatin**: An adipokine that can be pro-inflammatory
- **Lipocalin-2**: A pro-inflammatory adipokine that comes from adipocytes and macrophages
- **Interleukin 6**: An adipokine that can be pro-inflammatory
- **Tumor-necrosis factor**: An adipokine that can be pro-inflammatory
- **Interleukin 10**: An adipokine that can be anti-inflammatory
- **Transforming growth factor-β**: An adipokine that can be pro-inflammatory

Adipokines can affect insulin resistance, lipid and glucose metabolism, and inflammation. An imbalance of adipokines can lead to metabolic syndrome, type 2 diabetes, and cardiovascular disease.

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EPA Statement on Lead

Lead can be found in all parts of our environment – the air, the soil, the water, and even inside our homes. Much of our exposure comes from human activities including the use of fossil fuels including past use of leaded gasoline, some types of industrial facilities and past use of lead-based paint in homes. Lead and lead compounds have been used in a wide variety of products found in and around our homes, including paint, ceramics, pipes and plumbing materials, solders, gasoline, batteries, ammunition and cosmetics.

Lead may enter the environment from these past and current uses. Lead can also be emitted into the environment from industrial sources and contaminated sites, such as former lead smelters. While natural levels of lead in soil range between 50 and 400 parts per million, mining, smelting and refining activities have resulted in substantial increases in lead levels in the environment, especially near mining and smelting sites.

When lead is released to the air from industrial sources or spark-ignition engine aircraft, it may travel long distances before settling to the ground, where it usually sticks to soil particles. Lead may move from soil into ground water depending on the type of lead compound and the characteristics of the soil.

https://www.epa.gov/lead/learn-about-lead

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EPA Statement on Lead

Until recently, children were identified as having a blood lead level of concern if the test result is 10 or more micrograms per deciliter of lead in blood. Experts now use a new level based on the U.S. population of children ages 1-5 years who are in the top 2.5% of children when tested for lead in their blood (when compared to children who are exposed to more lead than most children). Currently that is 3.5 micrograms per deciliter of lead in blood. The new, lower value means that more children likely will be identified as having lead exposure allowing parents, doctors, public health officials, and communities to take action earlier to reduce the child's future exposure to lead.

https://www.epa.gov/lead/learn-about-lead

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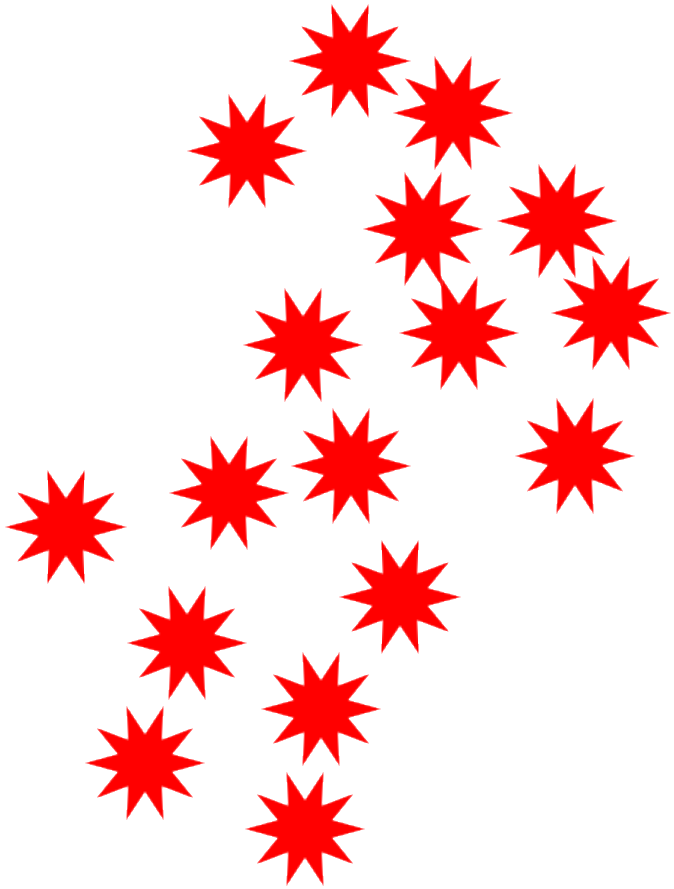
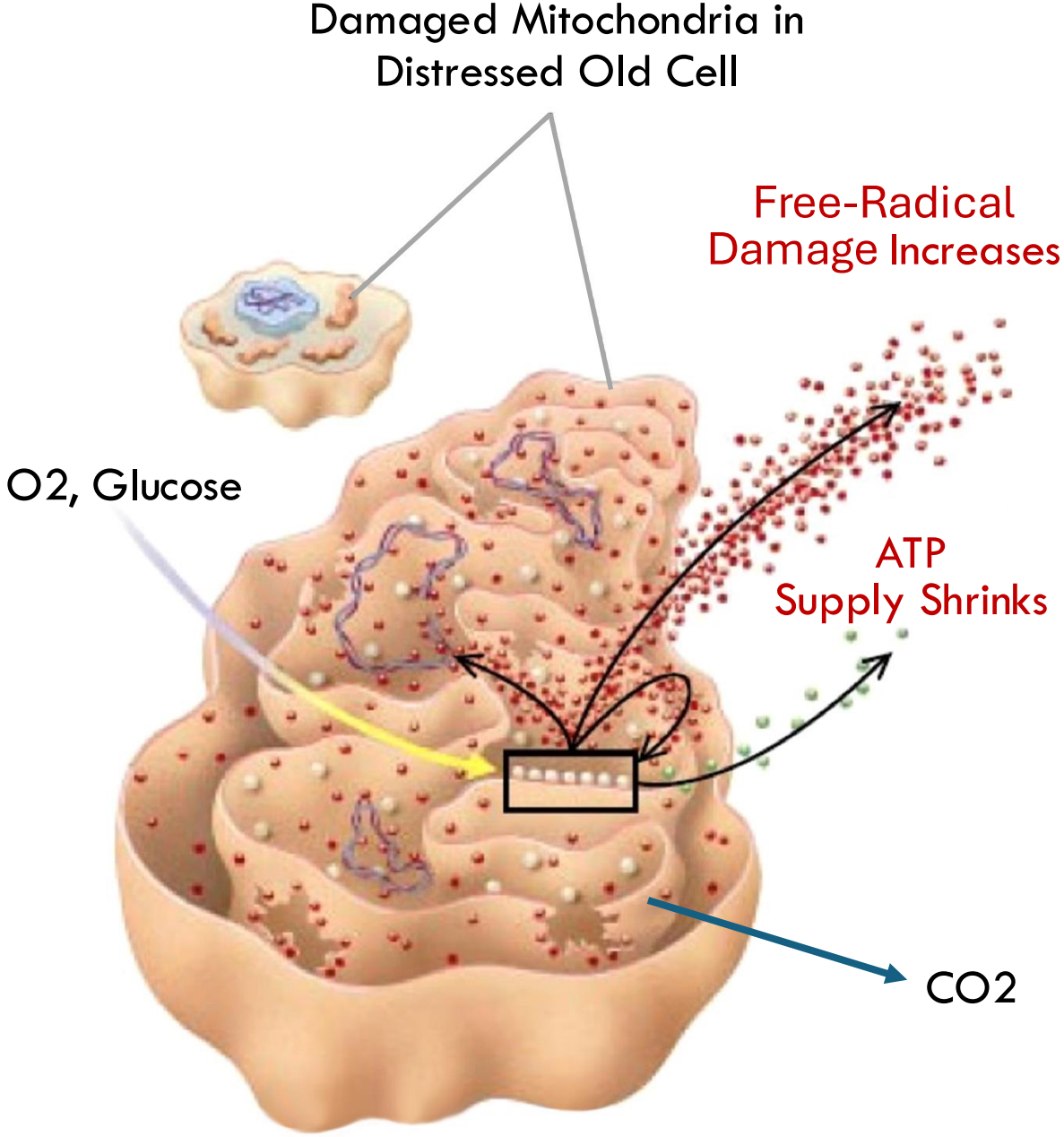
= Glucose Molecule



INSULIN



Review > Clin Chim Acta. 2007 Aug;383(1-2):57-64. doi: 10.1016/j.cca.2007.04.024.
Epub 2007 May 8.

Low level lead exposure and oxidative stress: current opinions

M Ahamed [1], M K J Siddiqui

Lead continues to pose a serious threat to the health of many children as well as adults. Concern about lead exposure as a significant public health problem has increased as evidence has mounted regarding adverse health effects at successively lower levels. This issue is complicated by the fact that there is no demonstrated biological function of lead in human. Lead potentially induces oxidative stress and evidence is accumulating to support the role of oxidative stress in the pathophysiology of lead toxicity. Lead is capable of inducing oxidative damage to brain, heart, kidneys, and reproductive organs. The mechanisms for lead-induced oxidative stress include the effects of lead on membranes, DNA, and antioxidant defense systems of cells. Recent epidemiological and toxicological studies have reported that lead exposure causes several diseases including hypertension, kidney disease, neurodegenerative disease and cognitive impairment. Although all these diseases include components of oxidative stress, the relevance of oxidative stress to lead-related diseases with low lead exposure has been criticized because most of the mechanistic studies have been conducted at moderate to higher dose levels. The association between low level lead exposure and oxidative stress has not been explored systematically. The present review focuses on mechanisms for lead-induced oxidative stress and relevance of oxidative stress to lead-related human disease with low lead exposure.

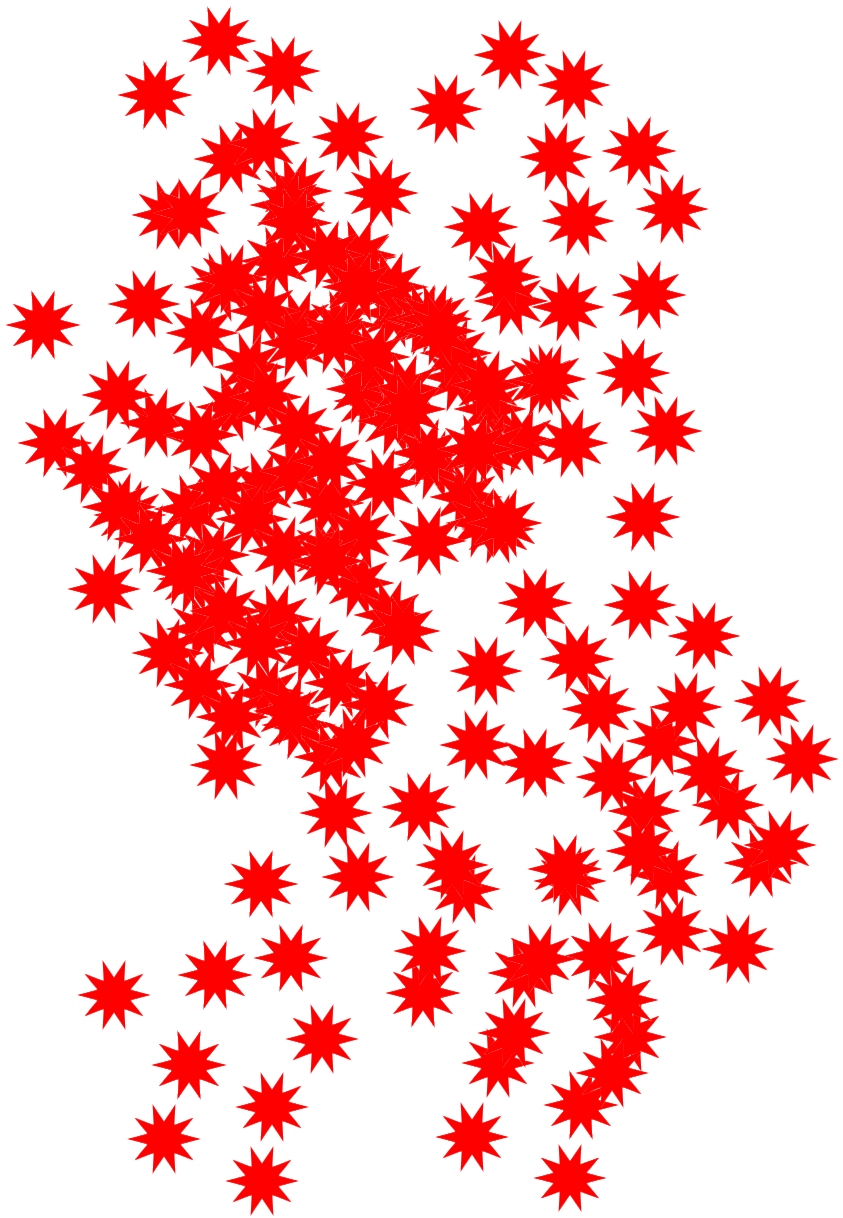
Toxics. 2018 Sep 6;6(3):54. doi: 10.3390/toxics6030054

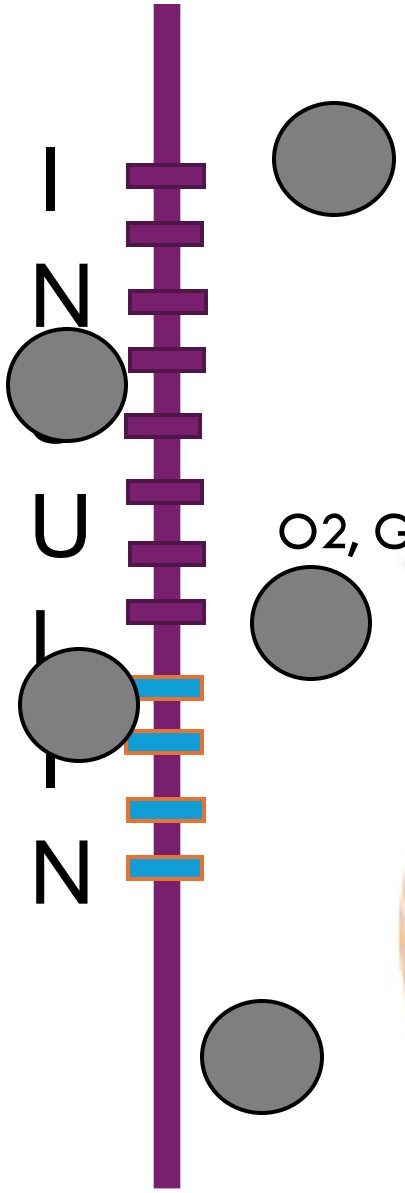
Diabetes and Exposure to Environmental Lead (Pb)

Todd Leff [1,2,3,*], Paul Stemmer [1,4], Jannifer Tyrrell [2,3], Ruta Jog [2,3]

Fatty liver, especially the form not associated with excessive alcohol consumption—known as NAFLD (non-alcoholic fatty liver disease) co-exists with type 2 diabetes. In some populations up to 70% of diabetic patients also have NAFLD [23,24], which makes NAFLD incidence a reasonable predictor of type 2 diabetes rates. Given the physiological relationship between these two syndromes, an observed correlation between fatty liver and lead exposure could suggest a causative link between exposure to lead and diabetes.

In a recent study of the population living in the Yangtze river delta in China, Zhai et al. found that elevated blood lead levels were associated with an increased risk of NAFLD in both men and women, although the association was significantly stronger in women [5]. Consistent with this NAFLD study is an earlier study carried out with data from the 2003–2004 NHANES cohort. Cave et al. observed correlation between blood lead levels and a general marker of liver disease—elevated serum alanine aminotransferase (ALT) [4]. Although altered ALT levels are associated with multiple types of hepatic dysfunction, the observation that they are elevated in lead-exposed individuals is consistent with there being a causative link between lead exposure levels and the kinds of liver dysfunction associated with diabetes,

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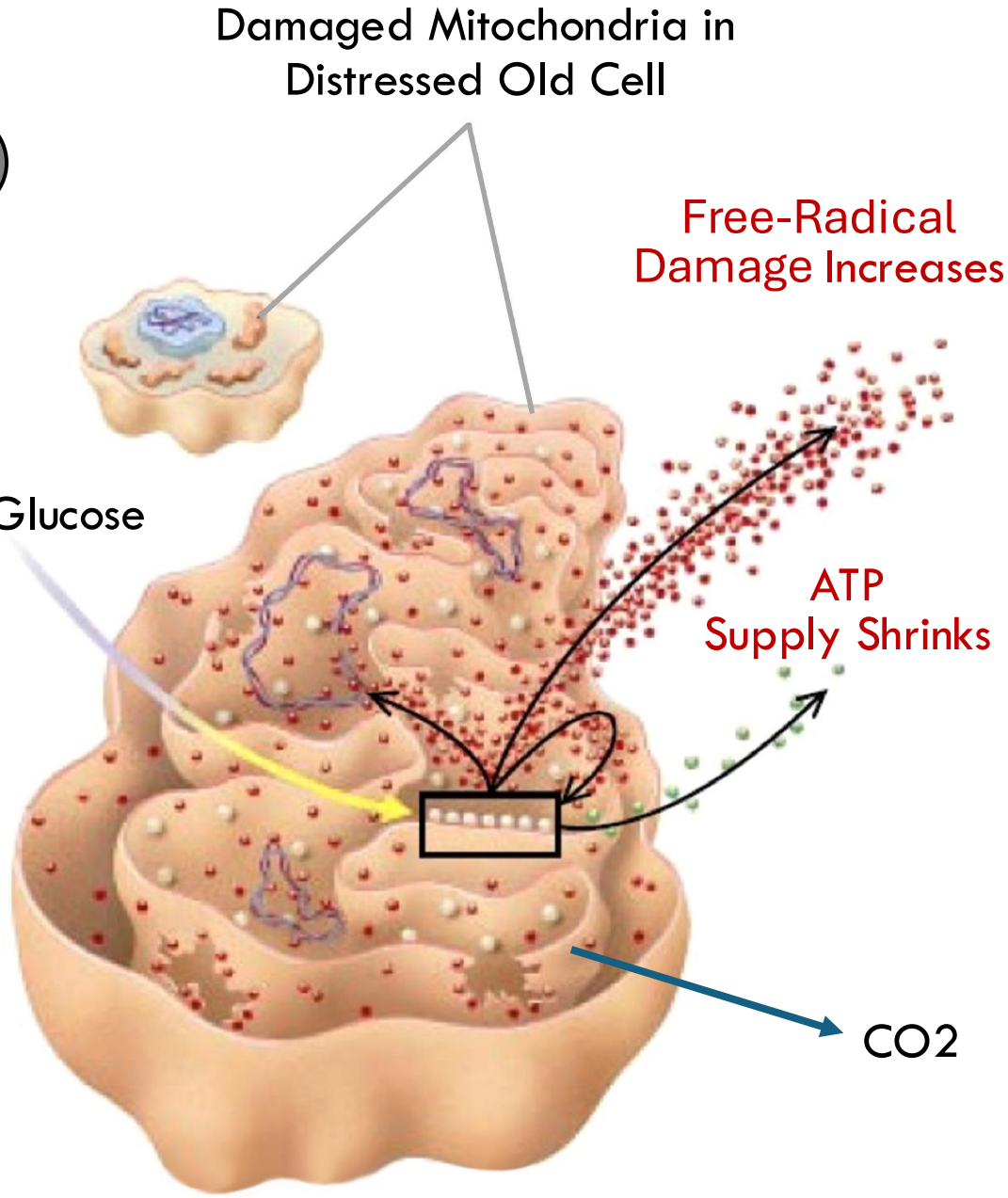
Damaged Mitochondria in
Distressed Old Cell
Free-Radical
Damage Increases
O2, Glucose
ATP
Supply Shrinks
CO2

Environmental exposure to lead and progressive diabetic nephropathy in patients with type II diabetes

J-L Lin[1], D-T Lin-Tan[1], C-C Yu[1], Y-J Li[1], Y-Y Huang[2] and K-L Li[2]

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Analytical results demonstrated that basal body lead burdens and blood lead levels, even when at low levels, were major risk factors in diabetic nephropathy progression in type II diabetic patients. The correlation between environmental lead exposure and progressive diabetic nephropathy was dose dependent, even after potentially related covariates were comprehensively adjusted. These findings are similar to those obtained in previous epidemiological work,[18] which found that a longitudinal decline of renal function among middle-aged individuals was dependent on both basal bone and blood lead levels; this effect was most pronounced in diabetic patients. However, this study is able to draw a more supportable conclusion than before as factors related to progressive renal function were adjusted during analyses and diabetic patients with possible primary renal diseases were strictly excluded. Mean blood lead level of this study patients was 6.5 μg/dl, a level similar to those obtained in a nationwide survey of blood lead levels in Taiwan (7.7 μg/dl)[19] and is situated between that of general population in Europe (11.4 μg/dl)[4] and America (2.8 μg/dl).[5] Mean body lead burden was 108.5 μg, far less than the upper normal limit (blood lead level was <20 μg/dl (0.97 μmol/l) in Taiwan and body lead burden was <600 μg (2.90 μmol)).[10] This study suggested that a single course of chelation therapy can significantly retard progression of diabetic nephropathy for at least 1 year, even when other treatable factors are controlled. These analytical findings indicate that chronic low-level environmental lead exposure can accelerate the progression of diabetic nephropathy in patients with type II diabetes.

Notably, no safe limits for lead indices were identified in this work. The influence of body lead burden on progressive renal insufficiency was more pronounced in diabetic nephropathy patients than in non-diabetic chronic renal disease patients; that is, each increase of 100 μg (0.48 μmol) in body lead burden reduced the glomerular filtration rate by 7.2 ml/min/year/1.73 m^2 of body surface area, 24 times a previously published reduction in the glomerular filtration rate in non-diabetic patients.[15] This analytical

Molecular mechanisms involved in lead induced disruption of hepatic and pancreatic glucose metabolism

Sara Mostafalou [a b], Maryam Baeeri [b], Haji Bahadar [b c], Mohammad Soltany-Rezaee-Rad [b], Mahdi Gholami [b], Mohammad Abdollahi [b]

Lead (Pb) is a toxic heavy metal known to be associated with pathology of various human chronic diseases. This study has focused on the effect of lead on glucose homeostasis with regard to metabolic function of pancreas and liver. Islets of Langerhans were isolated from the pancreas of rats and exposed to lead for 24h, then insulin release along with markers of ER stress and oxidative stress were evaluated. In another part, lead was administered to rats for 32 days and after evaluating criteria of diabetes, the activity of gluconeogenesis and glycogenolysis enzymes, and markers of oxidative stress and inflammation were measured in the liver. Lead disrupted insulin secretory function of islets through activating GSK-3β and ER stress, and increased activity of gluconeogenic enzymes in the liver featured by glucose intolerance. Chronic exposure to lead can disrupt glucose homeostasis by affecting pancreas and liver mainly through induction of insulin resistance.

Mayo Clinic observations and serum thresholds:

- High blood pressure
- Joint and muscle pain
- Difficulties with memory or concentration
- Headache
- Abdominal pain
- Mood disorders
- Reduced sperm count and abnormal sperm
- Miscarriage, stillbirth or premature birth in pregnant women

Serum lead concentration: 5mcg/dL considered unsafe

Medical Chelation Intervention thresholds:

Serum lead concentration: 45mcg/dL or greater (9x what's considered safe).

----> EDTA Therapeutic interventions.

https://www.mayoclinic.org/diseases-conditions/lead-poisoning/diagnosis-treatment/drc-20354723

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Moderate (75th-95th percentile)

Heavy Metals | Environmental Toxins

TEST NAME	CURRENT RESULT	PREVIOUS RESULT	CURRENT RESULT / PREVIOUS RESULT	REFERENCE
Arsenic*	48.62		0 11.9 52	≤52 ug/g
Beryllium*	0.25		0 0.2 0.76	≤0.76 ug/g
Cadmium*	0.63		0 0.29 0.8	≤0.8 ug/g
Cesium*	6.82		0 6.37 10.3	≤10.3 ug/g
Lead*	0.72		0 0.52 1.16	≤1.16 ug/g
2,2-bis(4-Chlorophenyl) acetic acid (DDA)	14.56		0 7.9 19	≤19 ug/g
Butylparaben*	0.47		0 0.25 4.39	≤4.39 ug/g
Dimethyl phosphate (DMP)*	28.57		0 9.1 33.6	≤33.6 ug/g
Dimethylthiophosphate (DMTP)*	8.54		0 5.91 33.7	≤33.7 ug/g
Triclosan (TCS)*	66.49		0 29.9 358	≤358 ug/g

* Indicates NHANES population data reference ranges.

70 yo female, dm2, hbp, hypercholesterolemia, NAFLD

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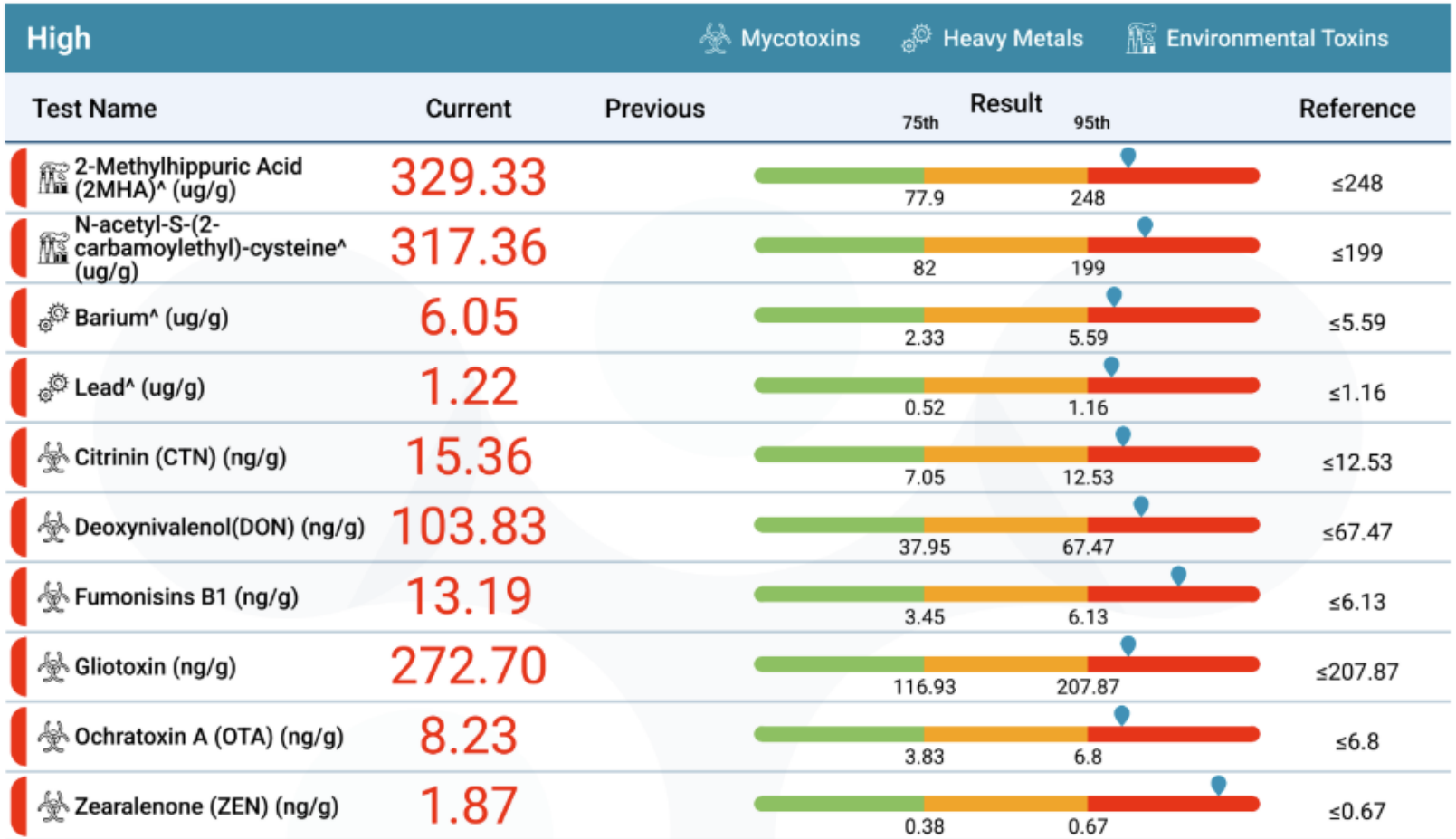

72 yo female, dm2, hbp, hypercholesterolemia, hypothyroidism

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Moderate (75th-95th percentile)

Mycotoxins Heavy Metals

TEST NAME	CURRENT RESULT	PREVIOUS RESULT	CURRENT RESULT / PREVIOUS RESULT	REFERENCE
Aflatoxin B1 (AFB1)	4.14		0 — 3.9 — 6.93	≤6.93 ng/g
Aflatoxin M1	5.85		0 — 3.6 — 6.4	≤6.4 ng/g
Gliotoxin	155.28		0 — 116 — 207	≤207.87 ng/g
Aluminum	32.44		0 — 17.8 — 45.1	≤45.15 ug/g
Arsenic*	12.62		0 — 11.9 — 52	≤52 ug/g
Barium*	4.16		0 — 2.33 — 5.59	≤5.59 ug/g
Lead*	0.56		0 — 0.52 — 1.16	≤1.16 ug/g

* Indicates NHANES population data reference ranges.

62 yo female, dm2, hbp, hypercholesterolemia, NAFLD

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73 yo female, dm2, hbp, neuropathy

Nutrient Elements

Element	Results	Prior	Recommended Limit	Units	Percentile Rank by Quintile (10 20 30 40 50 60 70 80 90)	Percentile
Calcium (Ca)	5.58	NA	4.7 - 6.4	mg/dL		52%
Copper (Cu)	104	NA	63 - 113	µg/dL		86%
Lithium (Li)	1.8	NA	< 0.1 - 21	µg/L		46%
Magnesium (Mg)	3.78	NA	2.93 - 4.17	mg/dL		74%
Manganese (Mn)	7.7	NA	4.26 - 14.3	µg/L		30%
Molybdenum (Mo)	< 0.2	NA	< 0.2 - 1.9	µg/L		NA
Selenium (Se)	178	NA	79 - 362	µg/L		31%
Zinc (Zn)	622	NA	454 - 745	µg/dL		61%

Whole Blood Element Ratios

Element	Results	Prior	Recommended Limit	Units	Percentile Rank by Quintile (10 20 30 40 50 60 70 80 90)	Percentile
Ca/Mg Ratio	1.48	NA	1.27 - 1.86	NA		35%
Cu/Zn Ratio	0.167	NA	0.103 - 0.193	NA		72%

Toxic Elements

Element	Results	Prior	Recommended Limit	Units	Percentile Rank by Quintile (10 20 30 40 50 60 70 80 90)	Percentile
Antimony (Sb)	6.4	NA	< 7.0	µg/L		83%
Arsenic (As)	1.9	NA	< 6.3	µg/L		46%
Cadmium (Cd)	0.3 B	NA	< 0.74	µg/L		46%
Lead (Pb)	1.43	NA	< 2.34	µg/dL		60%
Mercury (Hg)	0.6 B	NA	< 5.8	µg/L		29%

Potentially Toxic Elements

Element	Results	Prior	Recommended Limit	Units	Percentile Rank by Quintile (10 20 30 40 50 60 70 80 90)	Percentile
Cobalt (Co)	0.4 B	NA	< 2.0	µg/L		60%
Silver (Ag)	< 0.1	NA	< 2.6	µg/L		NA
Strontium (Sr)	275	NA	< 470	µg/L		89%

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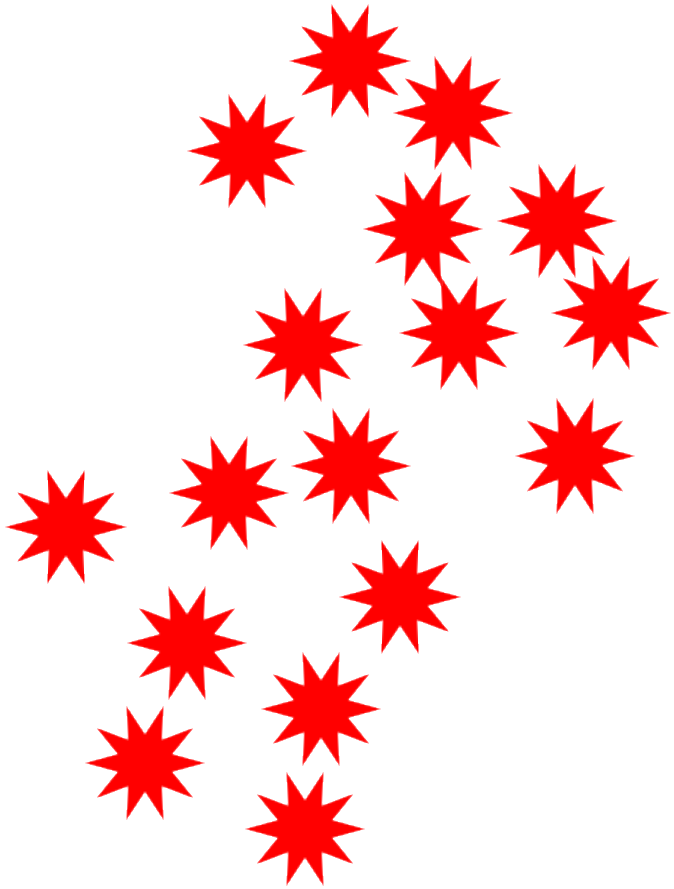
= Glucose Molecule



INSULIN