Casual Friday Series

Functional Blood Chemistry Series
Pt. 15: Oxidative Stress (I)

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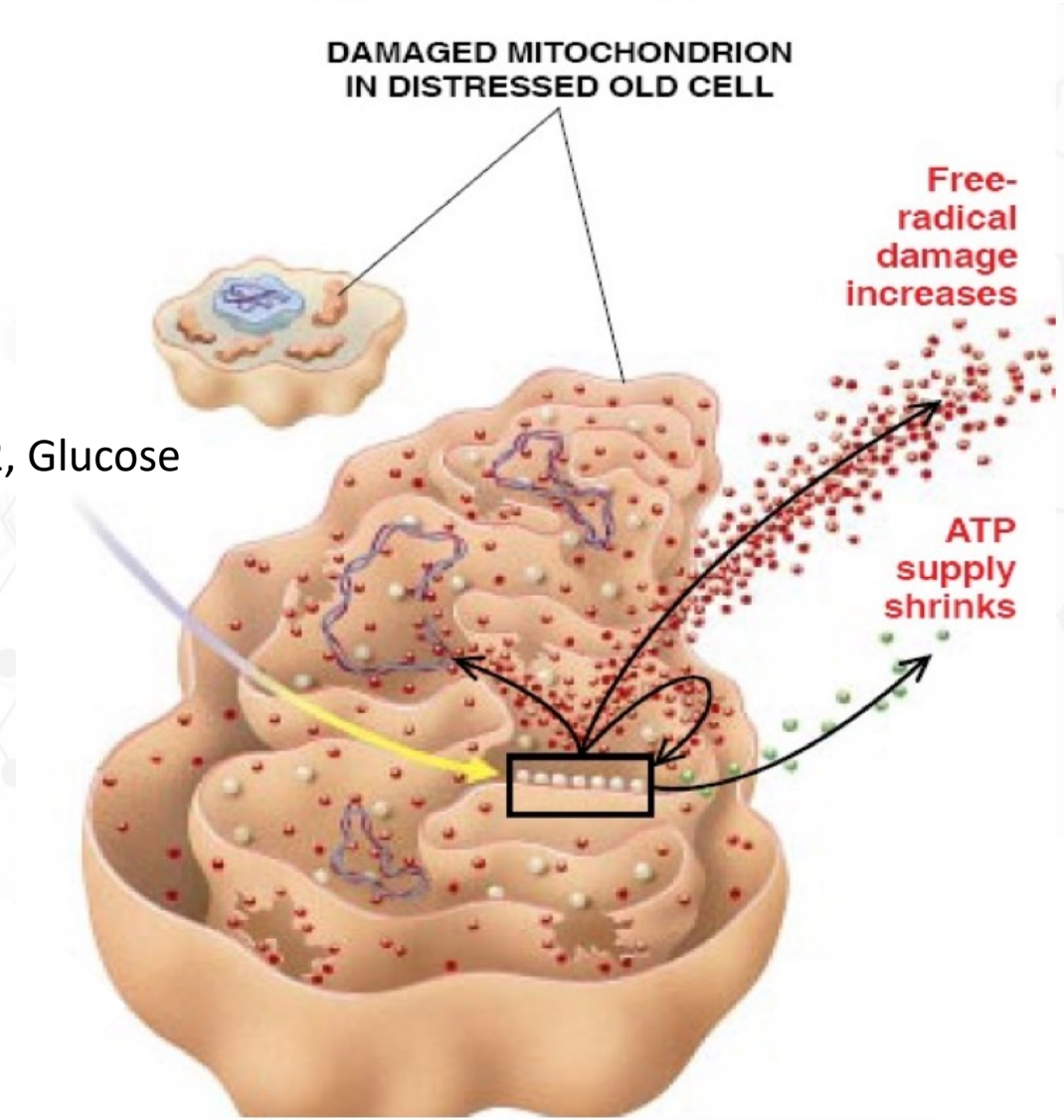

DAMAGED MITOCHONDRION
IN DISTRESSED OLD CELL
Free-
radical
damage
increases
ATP
supply
shrinks

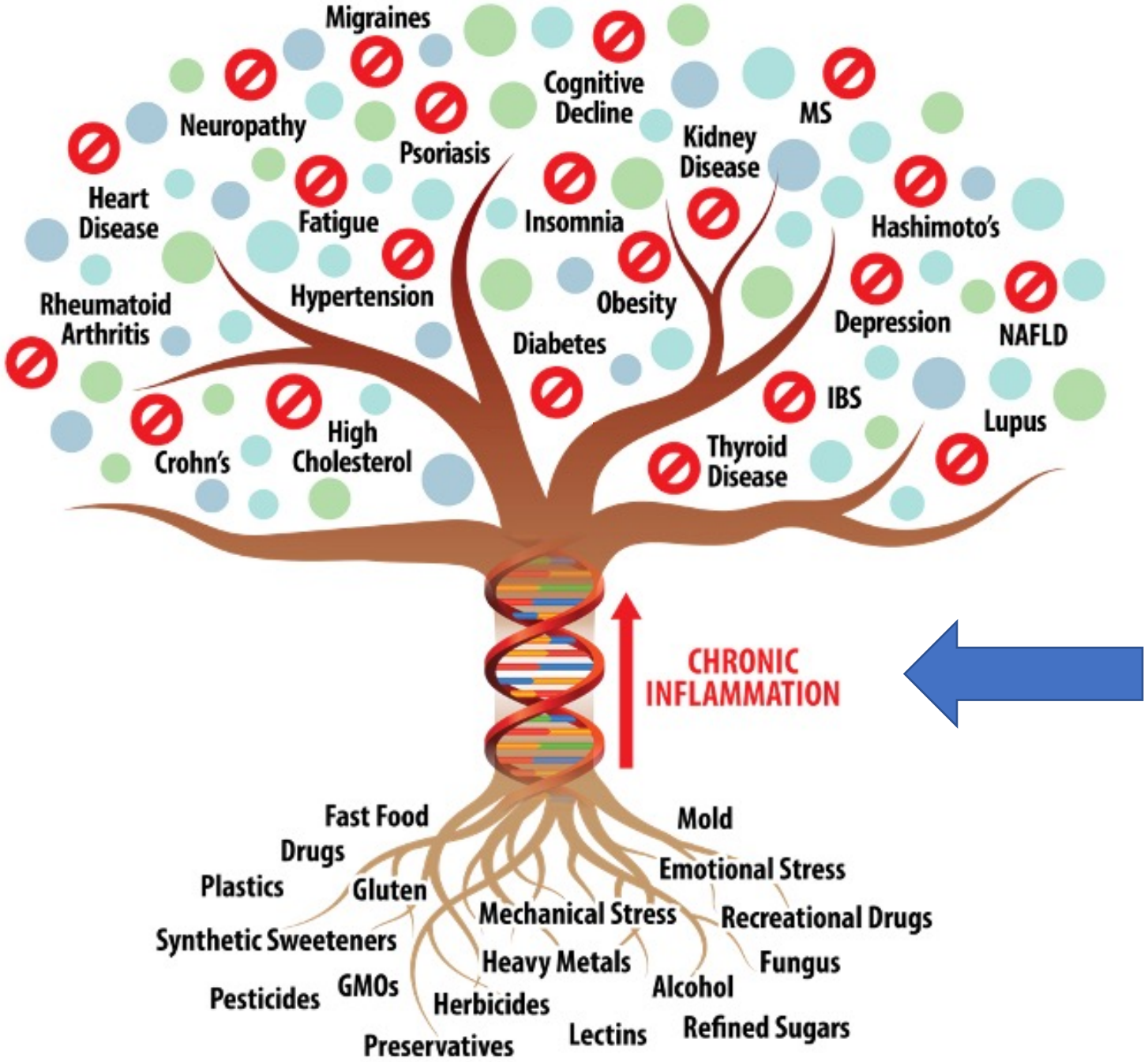
O2, Glucose

Oxidative Stress

Oxidative stress has been linked to heart disease, cancer, rheumatoid arthritis, hypertension, Alzheimer's disease, and Parkinson's disease…all the things.

Linked to inflammation and production of proinflammatory cytokines

Cytokines linked to diseases as well (osteoporosis, diabetes)

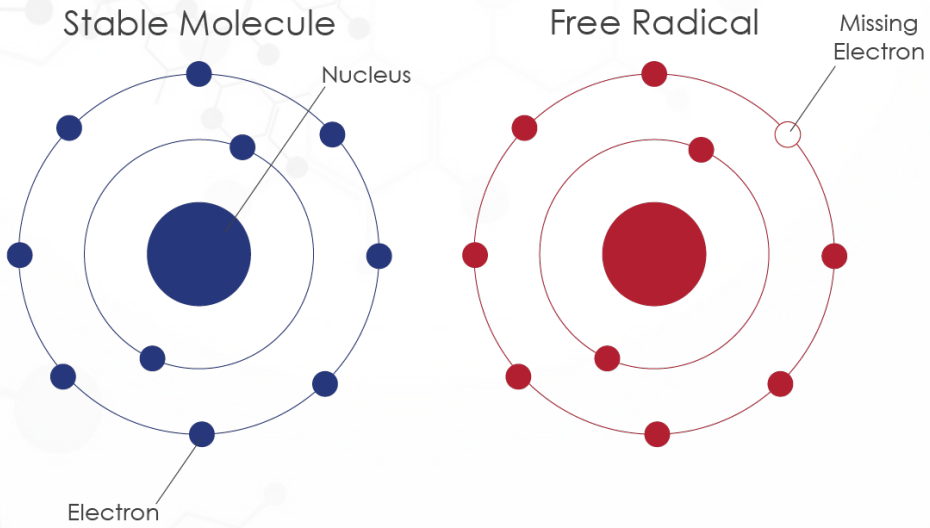

Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Alcohol
Herbicides
Refined Sugars
Lectins
Preservatives

Free Radicals

Oxidative stress is caused by excessive production of free radicals from oxygen (ROS) and nitrogen (RNS)

Atoms, molecules or ions with unpaired electrons

Highly reactive



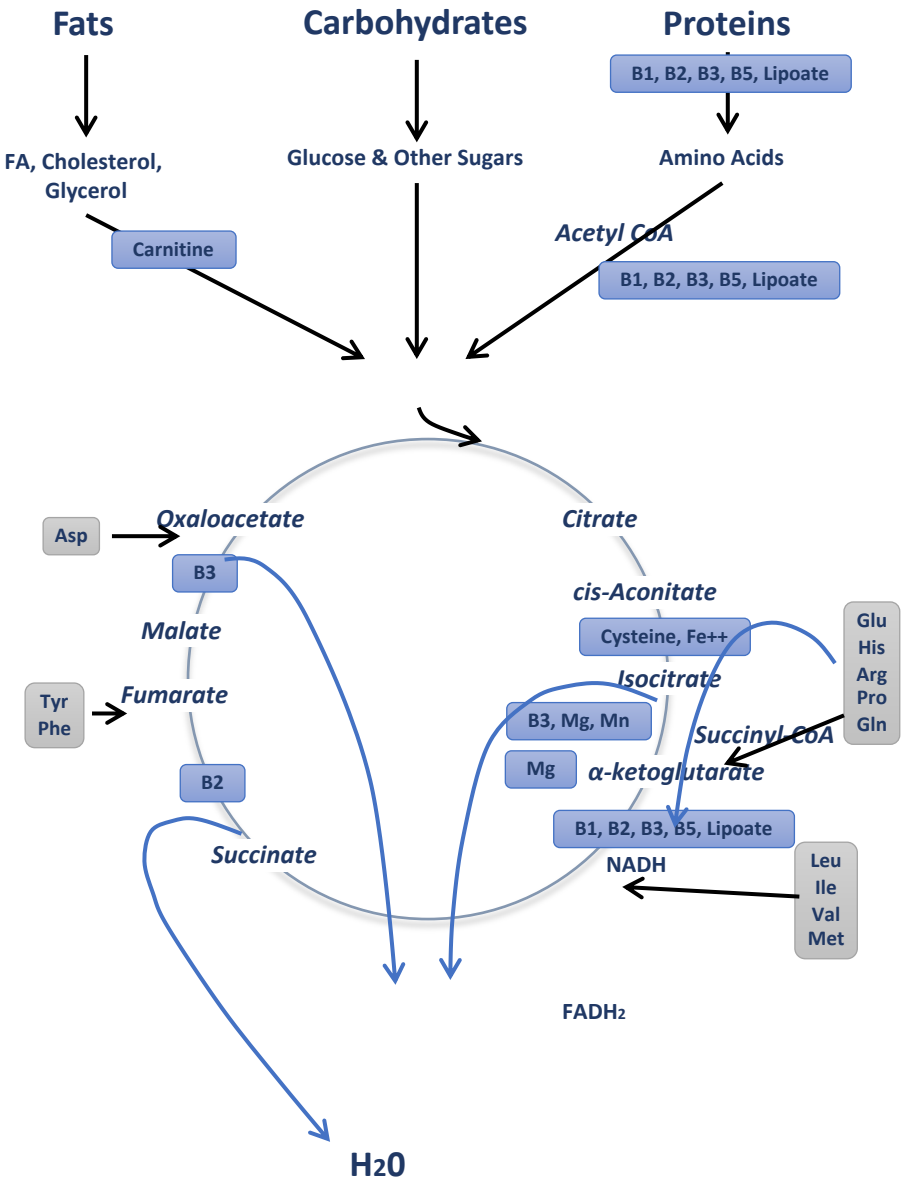
Examples include:

Hydroxyl radical (OH)

Peroxyl radical (ROO)

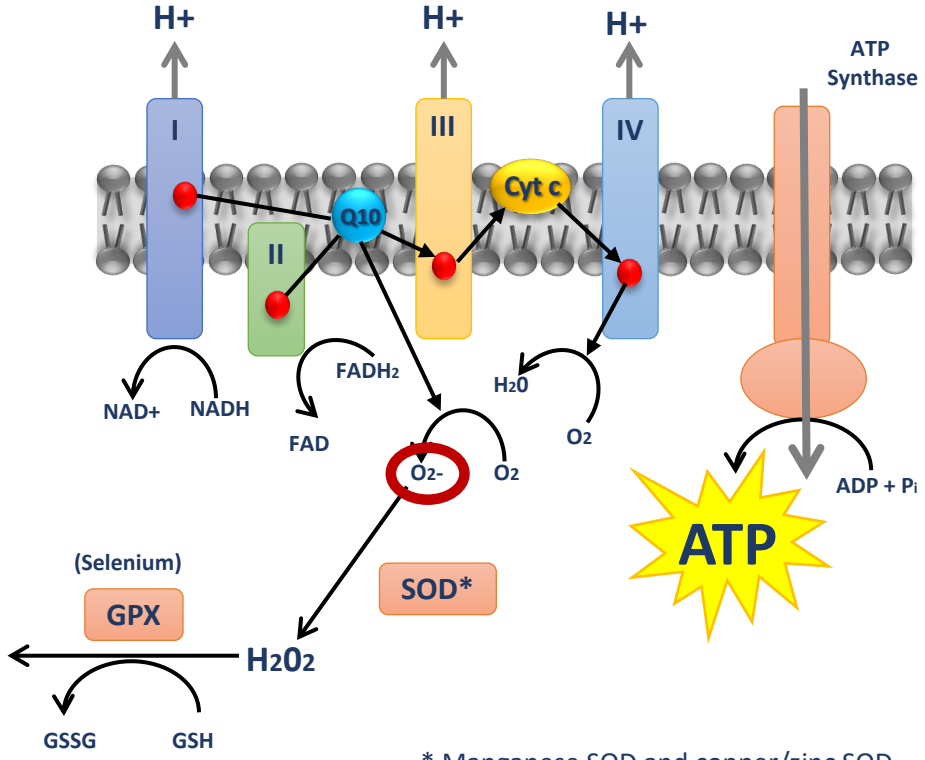
Superoxide radical (O2-)

Nitric oxide (NO), peroxynitrite (ONOO-), and NO2



Reactive oxygen species

- 0.4–4.0% of oxygen is converted to the superoxide (O2-) radical.
- Mitochondrial damage leads to more ROS, causing damage to mitochondrial DNA



* Manganese SOD and copper/zinc SOD

Causes of Free Radicals

Ionizing radiation

UV radiation

Metabolism (mitochondria)

Xenobiotics (pollution, toxin)

Inflammation

Medications

Diet

Stress

Exercise

Toxicity (bio/metal/enviro)

Conventional Markers of Oxidative Stress

Organelle	Biomarker activity
Nucleus	8-hydroxy deoxyguanosine
Mitochondria	Catalase, Cu/Zn SOD, Mn-SOD
Endoplasmic reticulum and golgi	PEG-SOD, F2-isoprostanes, HNE
Plasma	TBARS, CUPRAC, 8-iso-PGF(2a), LHP
Total cellular constituents	Cytokines, chaperones, telomeres

A + B = C = D = E

Lifestyle + Genetics = Organelle Dysfunction = Biomarker activity = Disease

Three Makers of Oxidative Stress

- Uric Acid
- GGT
- Bilirubin

Elisa Fabbrini,[1] Mauro Serafini,[2] Irena Colic Baric,[2] Stanley L. Hazen,[3] and Samuel Klein[1]

Effect of Plasma Uric Acid on Antioxidant Capacity, Oxidative Stress, and Insulin Sensitivity in Obese Subjects

We found that a marked decrease in serum UA levels caused a decrease in serum and saliva antioxidant capacity, assessed by TRAP and FRAP assays, and an increase in oxidative stress, assessed by measuring urinary isoprostanes and skeletal muscle protein carbonylation.

It is possible that an increase in UA concentration is a protective mechanism to attenuate the adverse effects of an increase in oxidative stress.

reduction of serum UA levels to 0 by infusing a recombinant urate oxidase. HUA subjects had 20–90% greater NEAC, but lower insulin sensitivity (40%) and levels of markers of oxidative stress (30%) than subjects in the NUA group (all $P < 0.05$). Acute UA reduction caused a 45–95% decrease in NEAC and a 25–40% increase in levels of systemic and muscle markers of oxidative stress (all $P < 0.05$), but did not affect insulin sensitivity (from 168 ± 25% to 156 ± 17%, P = NS). These results demonstrate that circulating UA is a major antioxidant and might help protect against free-radical oxidative damage.

myotubes and adipocytes (2,3), and suppress gene transcription of insulin in β-cells (5) and adiponectin in adipocytes (4).

Uric acid (UA) is a powerful scavenger of free radicals and provides ~60% of free-radical scavenging capacity in plasma (6). Although the antioxidant effect of UA suggests that it might have therapeutic effects, high serum UA concentration is associated with obesity and insulin resistance (7,8), and hyperuricemia has even been proposed as a component of the metabolic syndrome (9). However, it is possible that this increase in circulating levels of UA represents an adaptive response to protect

[1]Center for Human Nutrition and Atkins Center of Excellence in Obesity Medicine, Washington University School of Medicine, St. Louis, MO
[2]Agricultural Research Council-Research Centre on Food and Nutrition, Rome, Italy
[3]Center for Cardiovascular Diagnostics and Prevention, Department of Cell Biology, Lerner Research Institute, Cleveland Clinic, Cleveland, OH

Corresponding author: Samuel Klein, sklein@dom.wustl.edu.
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PLOS | ONE

RESEARCH ARTICLE

Elevated Serum Uric Acid Is Associated with Greater Bone Mineral Density and Skeletal Muscle Mass in Middle-Aged and Older Adults

Xiao-wei Dong☯, Hui-yuan Tian☯, Juan He, Chen Wang, Rui Qiu, Yu-ming Chen*

Guangdong Provincial Key Laboratory of Food, Nutrition and Health, School of Public Health, Sun Yat-sen University, Guangzhou 510080, People's Republic of China

☯ These authors contributed equally to this work.
* chenyum@mail.sysu.edu.cn

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Competing Interests: The authors have declared that no competing interests exist.

Abstract

Background and objective

Previous studies have suggested a positive link between serum uric acid (UA) and bone mineral density (BMD). In this study, we re-examined the association between UA and BMD and further explored whether this was mediated by skeletal muscle mass in a general Chinese population.

Method

This community-based cross-sectional study was conducted among 3079 (963 men and 2116 women) Chinese adults aged 40–75 years. Face-to-face interviews and laboratory analyses were performed to determine serum UA and various covariates. Dual-energy X-ray absorptiometry was used to assess the BMD and appendicular skeletal muscle mass. The skeletal muscle mass index (SMI = ASM/Height^2, kg/m^2) for the total limbs, arms, and legs was then calculated.

Results

The serum UA was graded and, in general, was significantly and positively associated with the BMD and muscle mass, after adjustment for multiple covariates in the total sample. Compared with participants in lowest quartile of UA, those participants in highest quartile showed a 2.3%(whole body), 4.1%(lumbar spine), 2.4%(total hip), and 2.0% (femoral neck) greater BMDs. The mean SMIs in the highest (vs. lowest) quartile increased by 2.7% (total), 2.5% (arm), 2.7% (leg) respectively. In addition, path analysis suggested that the favorable association between UA and BMD might be mediated by increasing SMI.

Serum uric acid levels in patients with myasthenia gravis are inversely correlated with disability

Dehao Yang[a,*], Yiyun Weng[a,*], Haihua Lin[b], Feiyan Xie[c], Fang Yin[e], Kangliang Lou[e], Xuan Zhou[e], Yixiang Han[d], Xiang Li[a] and Xu Zhang[a]

Uric acid (UA), the final product of purine metabolism, has been reported to be reduced in patients with various neurological disorders and is considered to be a possible indicator for monitoring the disability and progression of multiple sclerosis. However, it remains unclear whether there is a close relationship between UA and myasthenia gravis (MG), or whether UA is primarily deficient or secondarily reduced because of its peroxynitrite scavenging activity. We investigated the correlation between serum UA levels and the clinical characteristics of MG. We assessed 338 serum UA levels obtained in 135 patients with MG, 47 patients with multiple sclerosis, and 156 healthy controls. In addition, we compared serum UA levels when MG patients were stratified according to disease activity and classifications performed by the Myasthenia Gravis Foundation of America, age of onset, duration, and thymus histology (by means of MRI or computed tomography). MG patients had significantly lower serum UA levels than the controls ($P < 0.001$). Moreover, UA levels in patients with MG were inversely correlated with disease activity and disease progression ($P = 0.013$). However, UA levels did not correlate significantly with disease duration, age of onset, and thymus histology. Our findings suggest that serum level of UA was reduced in patients with MG and serum UA might be considered a surrogate biomarker of MG disability and progression. *NeuroReport* **27:301–305 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.**

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Keywords: disability, myasthenia gravis, uric acid

Departments of [a]Neurology, [b]Gastroenterology, [c]Surgical Oncology, [d]Laboratory of Internal Medicine, the First Affiliated Hospital of Wenzhou Medical University and [e]School of the First Clinical Medical Sciences, Wenzhou Medical University, Wenzhou, China

Correspondence to Xu Zhang, MD, Department of Neurology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, China
Tel: +86 577 555 79372; fax: +86 577 555 79318; e-mail: dizhangxu@126.com

*Dehao Yang and Yiyun Weng are co-first authors.

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Introduction

Myasthenia gravis (MG), caused by autoantibodies against the acetylcholine receptor (AChR) on the postsynaptic membrane at the neuromuscular junction, is an acquired autoimmune disease characterized by a defective transmission of nerve impulses to muscles [1]. Accumulating data have implicated oxidative stress in the immunopathogenesis of neuromuscular diseases [2,3].

As the final product of the common pathway of purine metabolism, uric acid (UA) is a naturally occurring antioxidant, with metal-chelating properties [4]. Previous studies have reported that UA can scavenge nitrogen radicals and superoxide, thus helping to block the generation of the strong oxidant peroxynitrite [5]. Peroxynitrite exerts toxic effects and irreversibly jeopardizes cellular metabolism and cell structures, including lipids, carbohydrates, protein, and DNAs [6]. Several studies have identified a therapeutic role of UA in experimental allergic encephalomyelitis and a beneficial function for increasing serum UA levels in multiple sclerosis (MS) patients [7,8]. Furthermore, UA might be a surrogate marker for monitoring MS activity [9].

Therefore, the aim of this study was to investigate whether the serum UA levels were decreased in MG patients and whether the decrease was associated with disease disability and progression.

Patients and methods

Serum samples were collected from 338 individuals: 135 patients with MG, 47 patients with MS, and 156 healthy controls (CTL). Venous blood was drawn from an antecubital vein in the morning after an overnight fast to measure the concentration of serum UA using a Clinical Analyzer Beckman Coulter AU5831 (Beckman Coulter, Brea, California, USA). In our hospital, the normal range of serum UA values is 208–428 μM for men and 155–357 μM for women. Simultaneously, concentrations of glutamate–pyruvate transaminase (normal range: 9–50 μM for men, 7–40 μM for women), glutamic–oxaloacetic transaminase (normal range: 15–40 μM, 13–35 μM for women), blood fasting sugar, and blood urea nitrogen were also measured using an enzymatic method on the same analyzer.

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Uric Acid ROS Summary

Elevated uric acid is associated with several conditions (i.e. hypertension, cardiovascular disease)

Elevated uric acid is also associated with increased Total Antioxidant Capacity (TAC)

Elevated uric acid can be due to fructose and alcohol consumption, dietary purine consumption, hyperinsulinemia, or poor renal clearance of UA

Elevated uric acid *may* indicate oxidative stress, and an attempt to attenuate oxidative stress by the body

Uric Acid ROS Summary

Decreased uric acid, on the other hand, may indicate unchecked oxidative stress

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URIC ACID: THE OXIDANT–ANTIOXIDANT PARADOX

Yuri Y. Sautin and **Richard J. Johnson**
Division of Nephrology, Hypertension and Transplantation, Department of Medicine, University of Florida, Gainesville, Florida, USA

Abstract

Uric acid, despite being a major antioxidant in the human plasma, both correlates and predicts development of obesity, hypertension, and cardiovascular disease, conditions associated with oxidative stress. While one explanation for this paradox could be that a rise in uric acid represents an attempted protective response by the host, we review the evidence that uric acid may function either as an antioxidant (primarily in plasma) or pro-oxidant (primarily within the cell).

The presence of ascorbic acid in the plasma is required for the antioxidant effect of uric acid. (lipid peroxidation)

Uric acid cannot scavenge all radicals, with superoxide as an example.

On the other hand, a vast literature on the epidemiology of cardiovascular disease, hypertension, and metabolic syndrome overwhelmingly shows that, at least among modern *Homo sapiens*, a high level of uric acid is strongly associated and in many cases predicts development of hypertension,[5–7] visceral obesity,[8–10] insulin resistance,[8,11,12] dyslipidemia,[8,11–13] diabetes type II,[11] kidney disease,[6] and cardiovascular and

Address correspondence to Richard J. Johnson, Division of Nephrology, Hypertension and Transplantation, Department of Medicine, University of Florida, P. O. Box 100224, Gainesville FL 32610-0224. johnsrj@medicine.ufl.edu.

Conflict of Interest: Dr. Johnson has patent applications related to the lowering of uric acid as a means for treating cardiovascular disease and obesity via the University of Florida and University of Washington.

Uric Acid + ROS

Traditional Reference range:

3.4-7.0 mg/dL (men)

2.4-6.0 mg/dL (women)

Optimal Reference Range:

3.7-5.5 mg/dL (men)

3.2-4.4 mg/dL (women)

GGT + ROS

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informa
healthcare

ORIGINAL ARTICLE

Gamma-glutamyltransferase predicts increased risk of mortality: A systematic review and meta-analysis of prospective observational studies

Y. Long[1], F. Zeng[2], J. Shi[3]*, H. Tian[3] & T. Chen[3]

[1]*Laboratory of Endocrinology and Metabolism, West China Hospital of Sichuan University, Chengdu, Sichuan, P. R. China,*
[2]*Department of Endocrinology, Dazhou Integrated Traditional Chinese and Western Medicine Hospital, Dazhou, Sichuan, P. R. China, and*
[3]*Department of Endocrinology and Metabolism, West China Hospital of Sichuan University, Chengdu, Sichuan, P. R. China*

Abstract

The aim of this study was to evaluate the association between gamma-glutamyltransferase (GGT) and mortality through a comprehensive analysis of existing evidence. PubMed, Embase, Chinese Biomedical Literature, and Science Citation Index databases were electronically searched. Studies were included if the study design was prospective and included reference and at-risk levels of GGT at baseline and mortality as a separate outcome. The quality of the studies included was assessed on the basis of Newcastle–Ottawa scale. Data from selected qualified studies were systematically reviewed, pooled, and analyzed according to the MOOSE guidelines and PRISMA statement. The results included the following: 1. 35 studies including 571 511 participants and 72 196 cases of mortality; 2. GGT, even at physiologic

kidney and liver and exists in serum and nearly all epithelial tissues [1]. GGT plays key roles in catabolism and synthesis of glutathione (GSH), the most important non-protein antioxidant outside the cell [1]. Changes in GGT are accompanied by an altered status of oxidative stress, a suggested common soil of many modern chronic diseases, such as metabolic syndrome [2], type 2 diabetes mellitus [3], hypertension [4], cancer [5], and cardiovascular diseases [6].

GGT was introduced to clinical laboratories nearly half a century ago and has become recognized as a biomarker of liver injury and alcohol consumption [1]. It was not until the 1990s that published studies began to suggest that GGT predicted death not only from alcohol-related illness but also from myocardial infarction, pointing out that GGT was an independent predictor of death and not merely a marker of alcohol consumption [1]. Lately, GGT has even been suggested to be a biomarker of transition across

design, have been few, mostly confined to special populations (especially alcoholics), and have considered GGT as a marker of alcohol consumption [1], which limited the understanding of GGT and mortality. In recent decades, plenty of prospective observational studies have been published. Most of these studies recruited more representable populations (e.g., free-living residence, patients with cardiovascular diseases or type 2 diabetes mellitus), some of which investigated the association between GGT and cause-specific death (e.g., cardiovascular death, cancer-related death). An increasing body of evidence has made it possible to perform a systemic analysis of the relationship between GGT and mortality. To this end, this study searched published data with prospective design on GGT and mortality and comprehensively analyzed their potential association following the guidelines of the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) [8].

*Graduated.
Correspondence: Tao Chen, Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, 37 GuoXue Street, Chengdu, Sichuan 610041, P. R. China. Tel: +86-15208203878. Fax: +86 28 85423459. E-mail: dr.chentao@gmail.com or chentao_2009@163.com

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The results included the following:

1. 35 studies including 571 511 participants and 72 196 cases of mortality;
2. GGT, even at physiologic levels, was associated with increased all-cause mortality and cardiovascular mortality, and might also be associated with cancer-related mortality in the general population

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Review

Elevated serum γ-glutamyltransferase activity is associated with increased risk of mortality, incident type 2 diabetes, cardiovascular events, chronic kidney disease and cancer – a narrative review

Giovanni Targher*

Section of Endocrinology, Department of Biomedical and Surgical Sciences, University of Verona, Verona, Italy

that are within the high-normal range, in risk prediction of incident type 2 diabetes, cardiovascular events, chronic kidney disease (CKD) or cancer, independent of alcohol consumption and other prognostic factors.

Several population based cohort studies have consistently shown that increased serum GGT activity, even high normal values within the reference range, is associated with an increased risk of major vascular and non-vascular outcomes
(especially incident type 2 diabetes and CVD morbidity and mortality) in both men and women, in different ethnic groups and among self-reported non-drinkers.

Keywords: cancer; cardiovascular disease; chronic kidney disease; diabetes; epidemiology; γ-glutamyltransferase.

Introduction

Serum γ-glutamyltransferase (GGT) enzyme activity has long been used as a reliable marker of liver dysfunction and excessive alcohol intake (1). However, in recent years our knowledge of the physiological functions of this enzyme has expanded and several important epidemiological associations have been reported.

This review critically appraises studies examining the prognostic value of serum GGT enzyme activity, even values

*Corresponding author: Dr. Giovanni Targher, Section of Endocrinology, Department of Biomedical and Surgical Sciences, University of Verona, Ospedale Civile Maggiore, Piazzale Stefani, 1, 37126 Verona, Italy
Phone: +39-045-8123748, Fax: +39-045-8027314,
E-mail: giovanni.targher@univr.it
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heavy chain in vitro. Presumably, in vivo the heavy chain not only secures the light chain to the cell membrane but also modifies its catalytic activity. There are up to eight potential sites for glycosylation, and the protein is heavily glycosylated with considerable heterogeneity (1–4). GGT does not have isoenzymes in the sense of proteins with different amino acid sequence but with the same catalytic function. However, there are a variety of GGT isoforms that differ in their carbohydrate content or structure (2–4). These isoforms may be separated by electrophoresis, isoelectric focusing, or by lectin-affinity chromatography. Much of the variation in electrophoretic mobility is due to the association of the isoforms with lipoproteins or immunoglobulin A (1). Indeed, several multiple forms of GGT have been described in serum. Most of these are large complexes between the enzyme and circulating lipoproteins or immunoglobulin A. Approximately 60%–80% of the total GGT in sera from patients with hepatobiliary diseases is complexed with lipoproteins. One dominant form of GGT is complexed with high-density lipoproteins (HDLs); a small, hydrophilic, form is also present in minor amounts (1).

GGT activity varies considerably between normal tissues and during stages of embryonic development. Hanigan and

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Review Article

Gamma-Glutamyltransferase: A Predictive Biomarker of Cellular Antioxidant Inadequacy and Disease Risk

Gerald Koenig[1,2] and Stephanie Seneff[3]

[1]*Health-e-Iron, LLC, 2800 Waymaker Way, No. 12, Austin, TX 78746, USA*
[2]*Iron Disorders Institute, Greenville, SC 29615, USA*
[3]*Computer Science and Artificial Intelligence Laboratory, MIT, Cambridge, MA 02139, USA*

Here, we examine the relationship of GGT to other serum markers such as serum ferritin (SF) levels, and we suggest a link to exposure to environmental and endogenous toxins, resulting in oxidative and nitrosative stress.

GGT is an early predictive marker for atherosclerosis, heart failure, arterial stiffness and plaque, gestational diabetes, and various liver diseases, including viral hepatitis, other infectious diseases, and several life-threatening cancers.

1. Introduction

A comprehensive review by Whitfield in 2001 [1] described GGT in its traditional role as a marker of liver dysfunction, bile duct conditions, and alcohol consumption. Some generalized or summary medical and scientific literature still describe GGT in those terms [2]. However, Whitfield had already extended that description to include elevated GGT in association with risk of coronary heart disease, type-II diabetes (T2D), and stroke [1]. Although gamma-glutamyl compounds include antioxidants, inflammatory molecules, drug metabolites, and neuroreactive compounds [3], the major function of GGT is enabling metabolism of glutathione and glutathionylated xenobiotics. However, elevated GGT levels, as noted by Whitfield and others, contribute to prooxidant activity, particularly in the presence of iron or copper [4, 5]. When GGT levels are elevated, damage to red blood cell membranes can occur causing the release of these potentially toxic transition metals, which can further result in chain, prooxidant reactions [6]. Increased levels of prooxidation can lead to downstream cell, tissue, and DNA damage caused by oxidative and nitrosative stress and the generation of deleterious reactive oxygen species or nitric oxide (ROS or NO) [7]. This combination of factors is observed with increasing frequency in many chronic diseases. Other investigators have added many newly identified GGT-related diseases and conditions to a rapidly growing list that very recently was modified by Sreeram et al. [8] to even include GGT as a marker for oxidative stress in periodontal disease.

In this paper, we review an extensive research literature on GGT as a marker for disease. Not only do we demonstrate strong potential for GGT to predict later disease risk, but we also show variations in GGT levels among different population groups (gender, ethnic, and regional) and show evidence of temporal upward trends in population level GGT

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Review Article

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Gerald Koenig[1,2] and Stephanie Seneff[3]

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[2]*Iron Disorders Institute, Greenville, SC 29615, USA*
[3]*Computer Science and Artificial Intelligence Laboratory, MIT, Cambridge, MA 02139, USA*

We hypothesize that GGT is a marker for glutathione depletion in the liver and that elevations in GGT reflect increased exposure to organic xenobiotics that are metabolized in the liver through glutathionylation.

We note that the population-wide level of GGT has been steadily increasing over time in the last three decades in the US and two decades in Korea. Several studies indicate this upward trend has affected other populations, including Europe, as well.

We suspect this may be indicative of increased exposure to environmental xenobiotics, especially POPs, as well as increased body iron burden.

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[2]*Iron Disorders Institute, Greenville, SC 29615, USA*
[3]*Computer Science and Artificial Intelligence Laboratory, MIT, Cambridge, MA 02139, USA*

The prevalence of several other clinical symptoms are correlated with GGT, including hypertension, insulin resistance, artery calcification, and albuminuria, as well as biological markers including lipids, creatine, triglycerides, uric acid, HbA1c, and hs-CRP. In many cases, GGT is a stronger predictor of disease risk than these other symptoms and markers.

its related disorders have risen in virtual lockstep. GGT is an early predictive marker for atherosclerosis, heart failure, arterial stiffness and plaque, gestational diabetes, and various liver diseases, including viral hepatitis, other infectious diseases, and several life-threatening cancers. We review literature both from the medical sciences and from life insurance industries demonstrating that serum GGT is a superior marker for future disease risk, when compared against multiple other known mortality risk factors.

1. Introduction

A comprehensive review by Whitfield in 2001 [1] described GGT in its traditional role as a marker of liver dysfunction, bile duct conditions, and alcohol consumption. Some generalized or summary medical and scientific literature still describe GGT in those terms [2]. However, Whitfield had already extended that description to include elevated GGT in association with risk of coronary heart disease, type-II diabetes (T2D), and stroke [1]. Although gamma-glutamyl compounds include antioxidants, inflammatory molecules, drug metabolites, and neuroreactive compounds [3], the major function of GGT is enabling metabolism of glutathione and glutathionylated xenobiotics. However, elevated GGT levels, as noted by Whitfield and others, contribute to prooxidant activity, particularly in the presence of iron or copper [4, 5]. When GGT levels are elevated, damage to red blood cell membranes can occur causing the release of these potentially toxic transition metals, which can further result in chain, prooxidant reactions [6]. Increased levels of prooxidation can lead to downstream cell, tissue, and DNA damage caused by oxidative and nitrosative stress and the generation of deleterious reactive oxygen species or nitric oxide (ROS or NO) [7]. This combination of factors is observed with increasing frequency in many chronic diseases. Other investigators have added many newly identified GGT-related diseases and conditions to a rapidly growing list that very recently was modified by Sreeram et al. [8] to even include GGT as a marker for oxidative stress in periodontal disease.

In this paper, we review an extensive research literature on GGT as a marker for disease. Not only do we demonstrate strong potential for GGT to predict later disease risk, but we also show variations in GGT levels among different population groups (gender, ethnic, and regional) and show evidence of temporal upward trends in population level GGT

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Review Article

Gamma-Glutamyltransferase: A Predictive Biomarker of Cellular Antioxidant Inadequacy and Disease Risk

Gerald Koenig[1,2] and Stephanie Seneff[3]

[1]*Health-e-Iron, LLC, 2800 Waymaker Way, No. 12, Austin, TX 78746, USA*
[2]*Iron Disorders Institute, Greenville, SC 29615, USA*
[3]*Computer Science and Artificial Intelligence Laboratory, MIT, Cambridge, MA 02139, USA*

Low antioxidant defenses are also correlated with elevated GGT, particularly reduced levels of glutathione. GGT is needed to metabolize glutathionylated xenobiotics in the liver and multiple other tissue sites including the lungs, and this is a simple explanation for its elevation in association with increased exposure to xenobiotics. GGT induces oxidative stress in the artery wall in the presence of free iron, and GGT also likely is an indicator of depleted supply of glutathione, especially in the liver, which leads to a cascade of problems related to increased oxidative stress.

GGT in its traditional role as a marker of liver dysfunction, bile duct conditions, and alcohol consumption. Some generalized or summary medical and scientific literature still describe GGT in those terms [2]. However, Whitfield had already extended that description to include elevated GGT in association with risk of coronary heart disease, type-II diabetes (T2D), and stroke [1]. Although gamma-glutamyl compounds include antioxidants, inflammatory molecules, drug metabolites, and neuroreactive compounds [3], the major function of GGT is enabling metabolism of glutathione and glutathionylated xenobiotics. However, elevated GGT levels, as noted by Whitfield and others, contribute to prooxidant activity, particularly in the presence of iron or copper [4, 5]. When GGT levels are elevated, damage to red blood cell membranes can occur causing the release of damage caused by oxidative and nitrosative stress and the generation of deleterious reactive oxygen species or nitric oxide (ROS or NO) [7]. This combination of factors is observed with increasing frequency in many chronic diseases. Other investigators have added many newly identified GGT-related diseases and conditions to a rapidly growing list that very recently was modified by Sreeram et al. [8] to even include GGT as a marker for oxidative stress in periodontal disease.

In this paper, we review an extensive research literature on GGT as a marker for disease. Not only do we demonstrate strong potential for GGT to predict later disease risk, but we also show variations in GGT levels among different population groups (gender, ethnic, and regional) and show evidence of temporal upward trends in population level GGT

GGT + ROS

Traditional Reference Range

0-65 IU/L

Optimal Reference Range

12-24 IU/L (Men)

10-22 IU/L (Women)

Do you Just Give them Glutathione?

ELSEVIER

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Biochemical Pharmacology

Glutathione catabolism as a signaling mechanism

Aldo Paolicchi[a], Silvia Dominici[b], Lisa Pieri[a], Emilia Maellaro[b], Alfonso Pompella[a,*]

[a]Department of Experimental Pathology, University of Pisa Medical School, Via Roma 55, 56126 Pisa, Italy
[b]Department of Pathophysiology and Experimental Medicine, University of Siena, Siena, Italy

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Abstract

Glutathione (GSH) is the main intracellular thiol antioxidant, and as such participates in a number of cellular antitoxic and defensive functions. Nevertheless, *non-antioxidant* functions of GSH have also been decribed, e.g. in modulation of cell proliferation and immune response. Recent studies from our and other laboratories have provided evidence for a third functional aspect of GSH, i.e. the *prooxidant*

Recent studies from our and other laboratories have provided evidence for a third functional aspect of GSH, i..e the *prooxidant* roles played by molecular species originating during its catabolism by the membrane ectoenzyme g-glutamyl transpeptidase (GGT)

The prooxidant reactions induced by GSH catabolism appear to represent a novel, as yet unrecognized mechanism for modulation of cellular signal transduction.

oxidative injury. Prooxidants thus can no longer be regarded as merely offensive species, and similarly, the physiological role of some established "antioxidants" also is in need of careful reconsideration. Glutathione (GSH)—perhaps the best known cellular antioxidant—appears an ideal candidate in this perspective. The *antioxidant* role of GSH is readily apparent in detoxification of electrophilic/oxidizing drugs and protection from lipid peroxidation.

*Corresponding author. Tel.: +39-50-554-851; fax: +39-50-554-929.
E-mail address: apompella@biomed.unipi.it (A. Pompella).

Abbreviations: AP-1, activator protein-1; AT-125, acivicin; ECL, enhanced chemiluminescence; EMSA, electrophoresis mobility shift assay; GGT, γ-glutamyl transpeptidase; gly-gly, glycyl-glycine; GSH, glutathione; GSH-DME, glutathione dimethyl ester; NF-κB, nuclear factor-κB; PARP, poly(ADP-ribose) polymerase; PP, protein phosphatase; ROS, reactive oxygen species; TNFR1, tumor necrosis factor-α receptor 1.

that prooxidant species (superoxide, H_2O_2, thiyl radicals) are produced during GSH catabolism, as a result of the interaction of GSH metabolites—cysteinyl-glycine in the first place—with trace levels of iron ions present in the cell environment. The interaction of these GSH/GGT-derived prooxidants several intra- and extracellular targets is responsible for appreciable modulatory effects on the signal transduction chains.

1. GSH, GGT and iron reduction

γ-Glutamyl transpeptidase (E.C. 2.3.2.2) is normally found in serum, and is expressed by a wide range of normal cell types [1,2] as well as in a number of neoplastic cell

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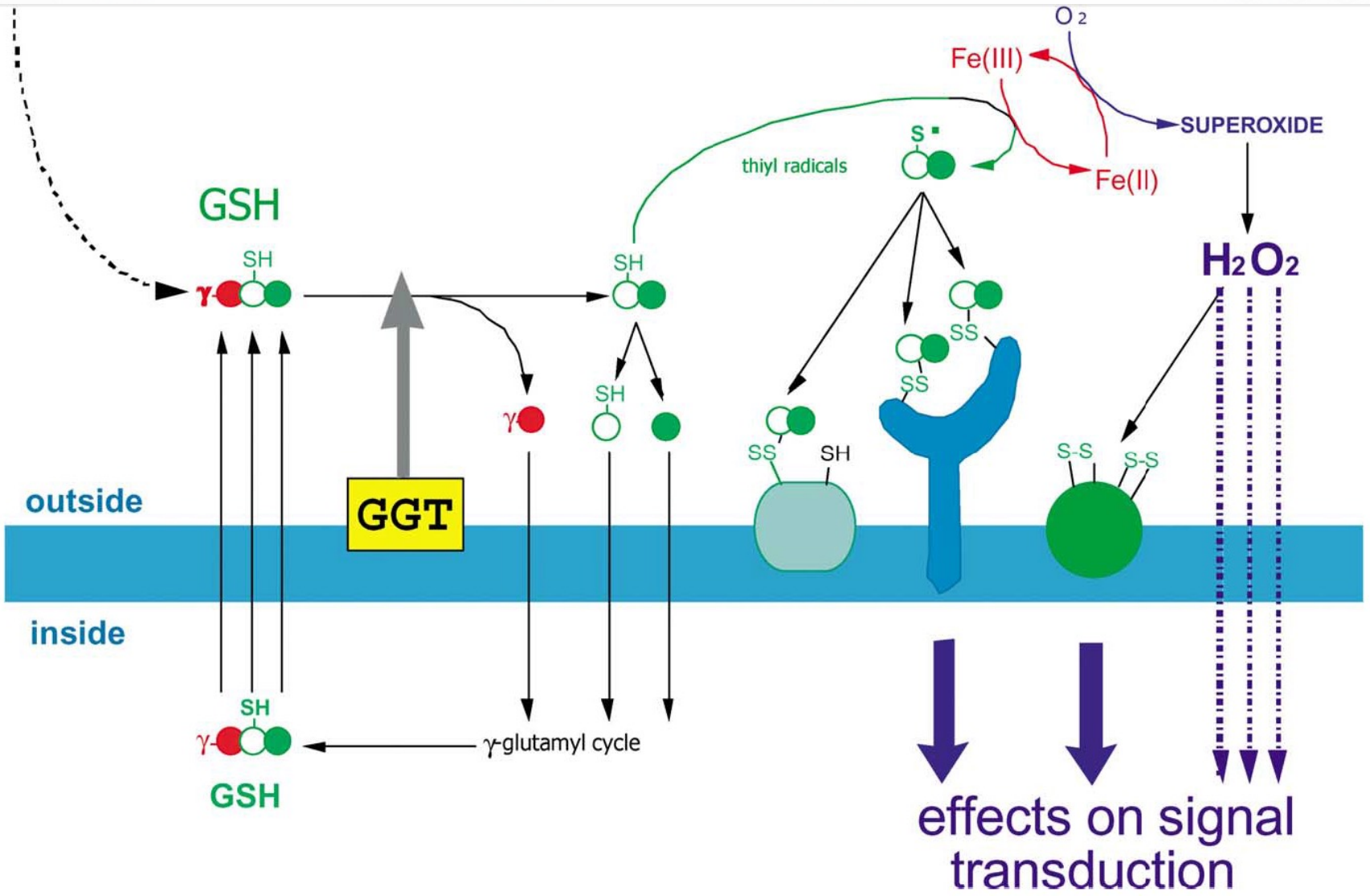

O 2
Fe(III)
SUPEROXIDE
thiyl radicals
Fe(II)
GSH
SH
γ
SH
H2O2
SS
SS
SH
γ
SH
SS
SH
S-S
S-S
outside
GGT
inside
SH
γ
γ-glutamyl cycle
GSH
effects on signal
transduction

Glutathione

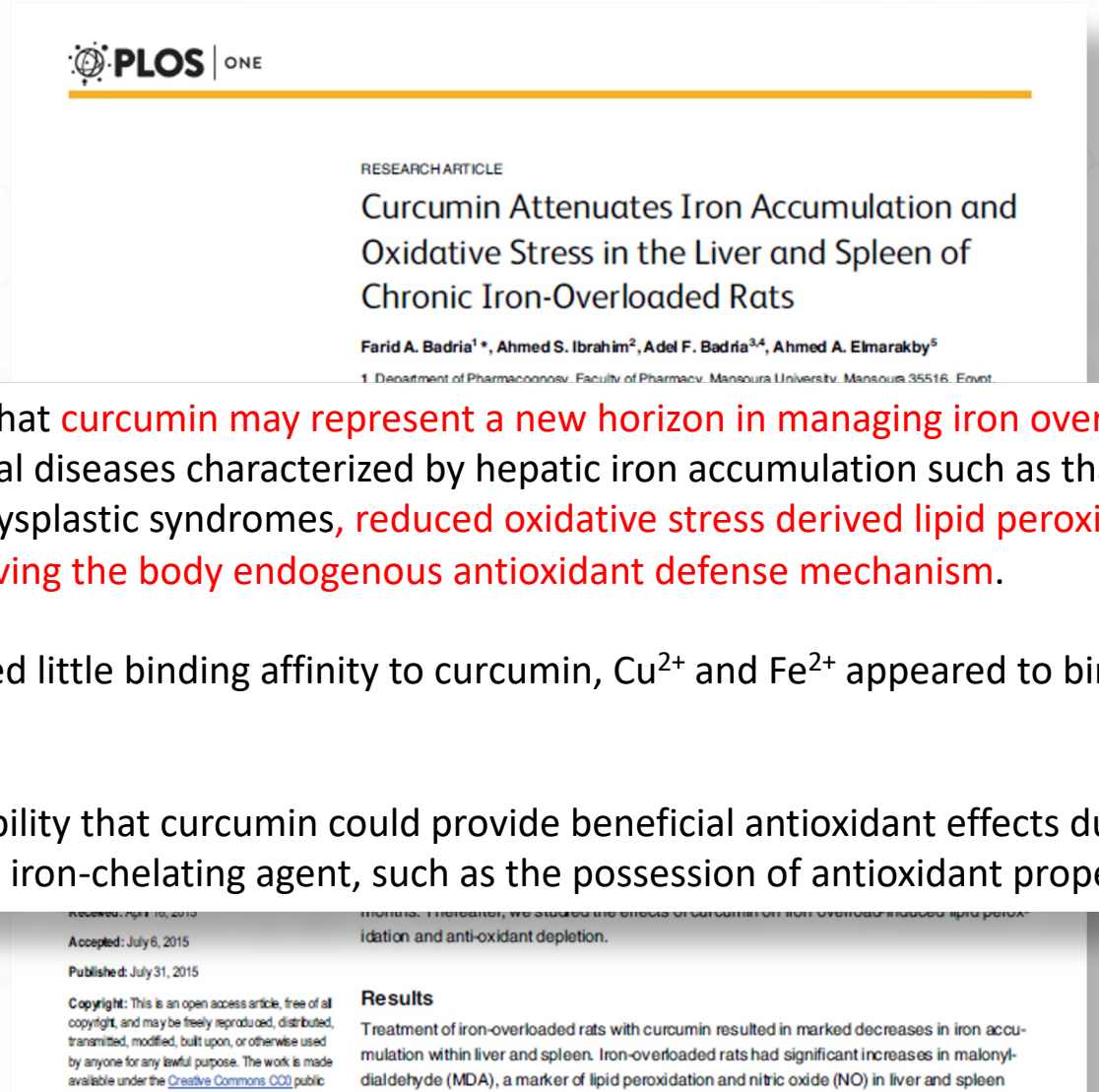
GGT produces cysteinyl glycine as a product of the decomposition of glutathione, and this dipeptide reacts with free iron to induce the Fenton reaction and subsequent production of superoxide, a well-established reactive oxygen species (ROS).

Glutathione

Elevated GGT levels, contribute to prooxidant activity, particularly in the presence of iron or copper.

When GGT levels are elevated, damage to red blood cell membranes can occur causing the release of these potentially toxic transition metals, which can further result in chain, prooxidant reactions.

Glutathione and Curcumin +



PLOS ONE

RESEARCH ARTICLE

Curcumin Attenuates Iron Accumulation and Oxidative Stress in the Liver and Spleen of Chronic Iron-Overloaded Rats

Farid A. Badria[1]*, Ahmed S. Ibrahim[2], Adel F. Badria[3,4], Ahmed A. Elmarakby[5]

1 Department of Pharmacognosy, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt

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idation and anti-oxidant depletion.

Results

Treatment of iron-overloaded rats with curcumin resulted in marked decreases in iron accumulation within liver and spleen. Iron-overloaded rats had significant increases in malonyldialdehyde (MDA), a marker of lipid peroxidation and nitric oxide (NO) in liver and spleen

Our study suggests that curcumin may represent a new horizon in managing iron overload-induced toxicity as well as in pathological diseases characterized by hepatic iron accumulation such as thalassemia, sickle cell anemia, and myelodysplastic syndromes, reduced oxidative stress derived lipid peroxide, possibly via iron chelation and improving the body endogenous antioxidant defense mechanism.

Although Zn^{2+} showed little binding affinity to curcumin, Cu^{2+} and Fe^{2+} appeared to bind at least two curcumin molecules.

This raises the possibility that curcumin could provide beneficial antioxidant effects during chronic iron overload beyond its role as an iron-chelating agent, such as the possession of antioxidant property.

Gamma-Glutamyltransferase (GGT)

Traditional Reference Range

0-65 IU/L

Optimal Reference Range

12-24 IU/L (Men)

10-22 IU/L (Women)

Bilirubin

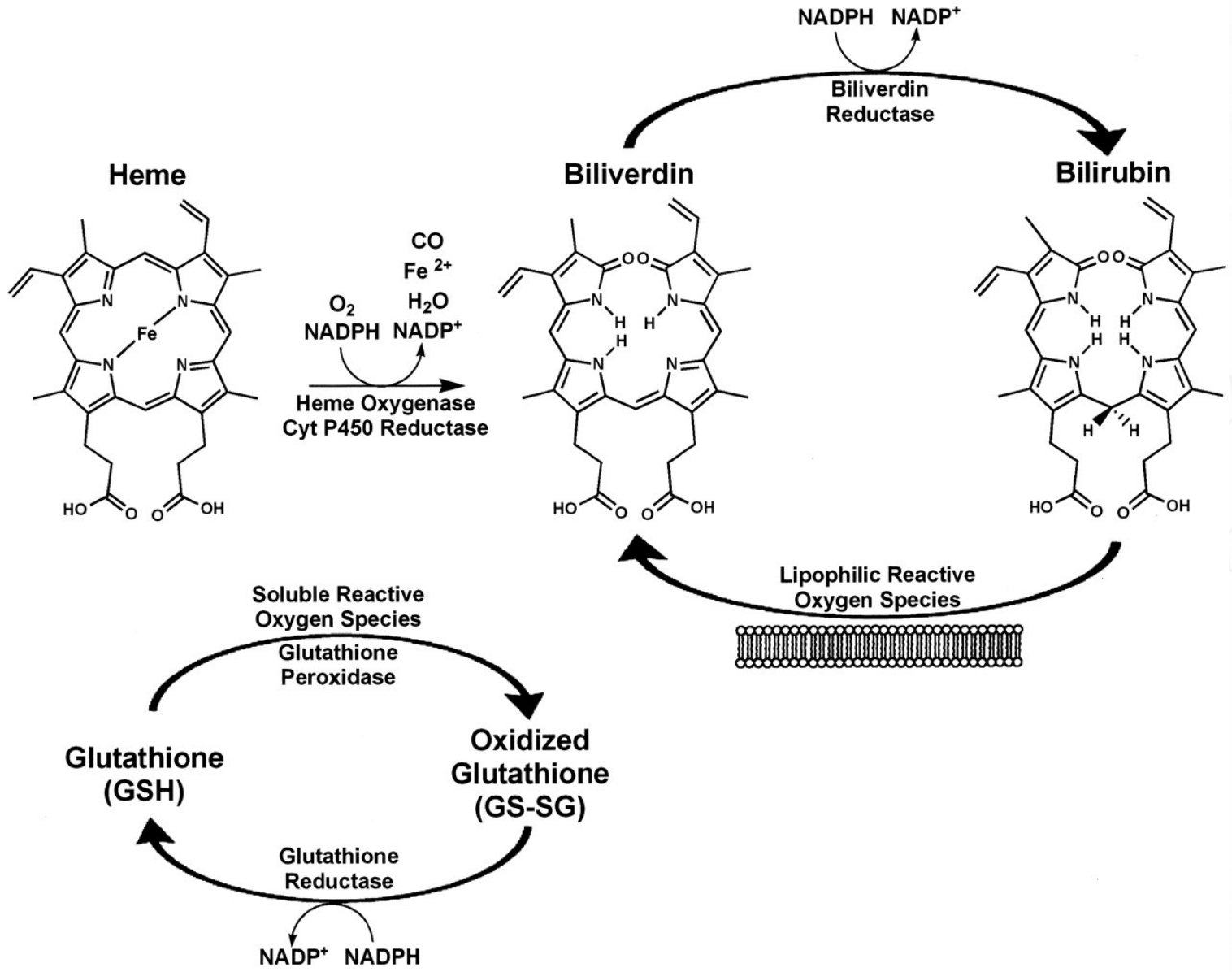
Bilirubin also functions as an antioxidant and thus may be decreased during oxidative stress

Bilirubin appears to be the most potent antioxidant against lipid peroxides

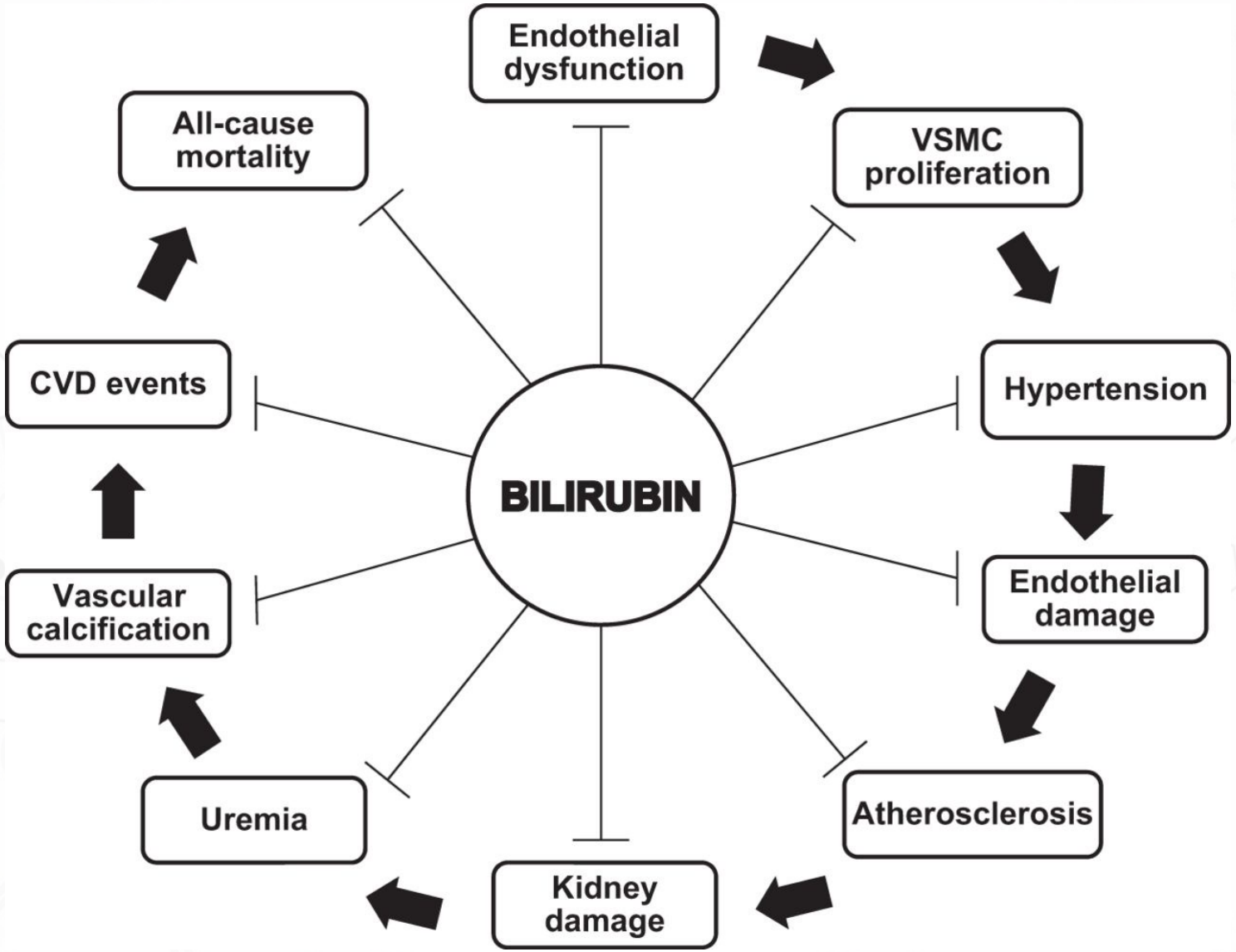
(Glutathione is hydrophilic)

Because of this, low bilirubin has also been associated with increased risk of cardiovascular disease and all cause mortality (death from all causes). Elevated levels may increase mortality as well.

Bilirubin may also increase insulin sensitivity and protect against future diabetes



Sedlak, Thomas W., and Solomon H. Snyder. 2004. “Bilirubin Benefits: Cellular Protection by a Biliverdin Reductase Antioxidant Cycle.” *Pediatrics* 113 (6): 1776–82.



Boon, Ai-Ching, Andrew C. Bulmer, Jeff S. Coombes, and Robert G. Fassett. 2014. “Circulating Bilirubin and Defense against Kidney Disease and Cardiovascular Mortality: Mechanisms Contributing to Protection in Clinical Investigations.” *American Journal of Physiology - Renal Physiology* 307 (2): F123–36. doi:10.1152/ajprenal.00039.2014.

Bilirubin

Traditional Reference Range

0.1-1.2 mg/dL

Optimal Reference Range

0.5 – 0.8 mg/dL

The Wedge Protocol