Your Gut 2.0: Unraveling Oxalate Intolerance

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This presentation is provided for educational and informational purposes only and does not constitute providing medical advice or professional services.

The information provided should not be used for diagnosing or treating a health problem or disease, and those seeking personal medical advice should consult with a licensed physician or healthcare provider.
Setting the Stage
Magnesium in Drinking Water

High Magnesium =
> 25 mg/L Mg^{2+}
= Heart Healthy
Major Minerals

[Diagram showing Ca\(^{2+}\) and Mg\(^{2+}\)]
Kidneys play a major role in Mg\(^{2+}\) homeostasis

Mg\(^{2+}\) inhibits calcification

Mg\(^{2+}\) deficiency is linked to the progression of CKD and other chronic diseases
Kidney Stone Disease
alternative terms:

Nephrolithiasis = nephro (kidney) + lithias (stone)

Urolithiasis = uro (urinary) + lithias (stone)
Urinary Stones - as old as time

Bladder stones more prevalent in earlier civilizations

Kidney stones notable increase in the last 100 years
  • 4-fold surge in last 50 years
  • 80% are CaOx

Global prevalence range - 5% to 20%
  • Rising in women and children
    • Pediatric increase 5-fold in last decade

Recurrence rate 50% in 5 years for adult

History, epidemiology and regional diversities of urolithiasis; López, M., & Hoppe, B., 2010
Kidney stone prevention; Peerapen, P. & Thongboonkerd, V., 2023
Human kidney stones: a natural record of universal biomineralization

Mayandi Sivaguru1,2,3, Jessica J. Saw1,3,4, Elena M. Wilson1,5, John C. Lieske6,7, Amy E. Krambeck8,9, James C. Williams10, Michael F. Romero6,11, Kyle W. Fouke12, Matthew W. Curtis13, Jamie L. Kear-Scott13, Nicholas Chia10,14 and Bruce W. Fouke1,2,5,15,16,17

Water, Minerals, & Microbes

Bio-mineralization

Human kidney stones: a natural record of universal biomineralization; Sivaguru, M., et al., 2021
Bacteria Create Fossils

1. Bacterial Cell
   Water envelope

2. Ca+2
   Bacterial Cell
   Ca+2

3. Ca+2
   Bacterial Cell
   Ca+2
   Ca+2
   Ca+2
   Ca+2
   Ca+2
   Ca+2

4. Bacterial Cell

Normal environment
Mineral concentration
Supersaturation
Precipitation
Crystal growth

Bio-mineralization

Photo by Robert Thiemann on Unsplash

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Kidney stones similar to other bio-mineralization forms - in natural and manmade environments.

All forms are significantly influenced by microorganisms (microbiome).
Kidney Stone Disease

> 80% of stones composed of Calcium Oxalate crystals

97.2% of stones contain Bacteria
70% are multi-antibiotic resistant

Linked to several systemic disorders -

CVD
Diabetes
Obesity
MetS
IBD
Crohn’s

Recent advances on the mechanisms of kidney stone formation (Review); Wang, Z., et al., 2021
The Use of Antibiotics and Risk of Kidney Stones; Joshi, S., & Goldfarb, D., 2019
Search “gut microbiome”

Articles per year

Next-Generation Technology

OLD MODEL
HOST
CONVENTIONAL FACTORS: Diet, Exercise, Lifestyle, etc.

NEW MODEL
HOST
MICROBIOME
DIET
Environmental Factors

HOLOBIONT
“Whole Unit of Life”
Bacteria Adapt Quickly

150x more genetic content than human
• Greater ability to survive critical environmental changes
• Radically faster than human genetic evolution

Aging, frailty, and the microbiome—how dysbiosis influences human aging and disease.
Haran, J., & McCormick, B., 2021
Diet rapidly and reproducibly alters the human gut microbiome

Lawrence A. David, Corinne F. Maurice, Rachel N. Carmody, David B. Gootenberg, Julie E. Button, Benjamin E. Wolfe, Alisha V. Ling, A. Sloan Devlin, Yog Varma, Michael A. Fischbach, Sudha B. Biddinger, Rachel J. Dutton & Peter J. Turnbaugh

2 to 5 days
Bacterial Metabolites

~ 30% of blood metabolites are produced by gut microbes
  SCFAs
  Hormones
  Vitamins

Microbiota produce, modify, and influence vitamin absorption

“Pantryome” concept - bacteria can take, donate, or share metabolites with other bacteria - crosstalk

Bidirectional micronutrient - microbiome axis

Vitamins as regulators of calcium-containing kidney stones—new perspectives on the role of the gut microbiome.
Chmiel, J., et al., 2023
Dysbiosis = Losing Diversity

Gain of function - acquired microbial functions that cause disease

Loss of function - loss of microbes and their beneficial functions

Difficult to detect due to lack of growth pattern

KSD is a good example of loss of function

Loss of function dysbiosis associated with antibiotics and high fat, high sugar diet. Miller, A., et al., 2019
Dysbiosis

Microbiota in health and diseases. Hou, K., et al., 2022

Fig. 4 Human microbiota dysbiosis contributes to various diseases
Humans lack enzymes to degrade oxalate

Over-accumulation of oxalate leads to toxicity

KSD is the most common form of oxalate toxicity

Microbes can degrade oxalate through multiple pathways

KSD provides a direct link between the gut and disease

Loss of function dysbiosis associated with antibiotics and high fat, high sugar diet. Miller, A., et al., 2019
Ancestral Oxalate Consumption?
Cactaceae Family

High CaOx crystal concentrations

About 2000 different species

Native to America
  • From northern Canada to The Patagonia
  • From sea level to Peruvian mountains
Pervasiveness of Phytoliths in Prehistoric Southwestern Diet … Dental Microwear. Reinhard, K., & Danielson, D., 2005
Mescalero Apache Women

Roasting Agave Hearts, 1900

Ethnohistoric records of Hunter-gatherer diet Lower Pecos, Riley, T., 2018
The Induction of Oxalate Metabolism In Vivo Is More Effective with Functional Microbial Communities… Miller, A., et al., 2017

Gut microbiota degrades ~100% of the oxalate consumed

High Oxalate Diet

White-throated woodrat (Neotoma albigula)

© 2019 Margaret Doolin
Inuits Eat Plants - High Oxalate

> 1000 edible plant species

Freezing
Dehydration
Slow-cooking
Baking, steaming, boiling
Oil-pack
Fermenting

“Eskimo ice cream”

Greens, berries, and roots
Wild celery
Tall cottongrass
Lichen and moss
Algae, kelp, seaweed

Photo by Jesse Brack on Unsplash

Africans Eat Plants - High Oxalate

- Cassava
- Sweet potato
- Cowpea
- Pigweed
- Pumpkin
- African cabbage
- Malabar spinach
- Nightshade berries

Oxalate Levels in Selected African Indigenous Vegetable Recipes... Wakhanu, J., et al., 2015
Mediterranean Wild Vegetables

The Mediterranean basin is characterized by an enormous biodiversity and a rich heritage of edible wild plants, which since Ancient times have represented an important source of nutrients for rural communities, both for food and medicinal uses.

… Oxalic acid was the most relevant organic acid found in the analyzed samples, due to its role as an antinutrient.

… The boiling process can reduce the amount of the antinutrient oxalic acid in wild greens.
Oxalate Foe or Friend?
Oxalates in Nature

- **Oxalogenic FUNGI**
- **Oxalogenic Trees**
- **Oxalotrophic BACTERIA**

**CALCIUM OXALATE**

**TURN OXALATES INTO CARBONATES**

**CO₂ fixed as soil carbon**

**↓ CO₂ emissions**

**↑ organic soil carbon**

Oxalate Carbonate Pathway—Conversion and Fixation of Soil Carbon... Syed, S., et al., 2020

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Fungi produce Oxalic acid

Bacteria consume Oxalate

Oxalate is the most oxidized carbon compound after CO₂
Bacteria and fungi
Shape biological life above and below ground

Bacteria Degrade

↑ pH

Bacteria alone convert strong acid (Oxalate) to weaker one

Fungi Produce

↓ pH

Oxalate increases micronutrient availability for plant uptake

Oxalate function in humans?
Three potential roles in human physiology

Stimulate the absorption of water, sodium, and chloride in kidney tubules

Assist in immune function to enhance phagocytosis through the production of H2O2

Contribute to RNA synthesis through formation of uracil and orotic acid
Oxalate in Humans

Liver
GENERATE
60 - 80%

Gut
ABSORB
10 - 15%

ENDOGENOUS

EXOGENOUS

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Up to 98% used by gut bacteria for energy

Intake critical for Oxalate homeostasis

Calcium binds to make Oxalate insoluble = crystalline

5 - 10% Excreted in feces
OXALATE PRODUCTION 60 - 80%

Glucose
(amino acids)

Glyoxal

Glyoxylate

OXALATE

URINARY OXALATE

Glyoxal Formation and Its Role in Endogenous Oxalate Synthesis, Lange, J., et al., 2012

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OXALATE EXCRETION

~ 95%

Oxalate Excreted via

Nephron

Glomerulus

Tubule

Waste Blood

Filtered Blood

Urine

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Healthy Kidneys

Glomerular Filtration Rate (GFR) > 90 mL/min

GFR ↓ 1% per year after age 40

Nephron number varies by individual

Total nephron number set in utero by 36 weeks

Human nephron number, hypertension, and renal pathology. Kanzaki, G., et al., 2020
Oxalate dysfunction in humans?
Hyperoxaluria

Pathways to hyperoxaluria:

1. ↓ kidney function - supersaturation
2. ↑ intestinal absorption
3. ↑ liver production

OXALATE ACCUMULATION

Contribution of Dietary Oxalate and Oxalate Precursors to Urinary Oxalate Excretion. Crivelli, J., et al., 2020
Supersaturation

- Driving force for CaOx crystal growth
- Main risk factor for stone formation
- Linked to low water intake
Glyoxal Formation and Its Role in Endogenous Oxalate Synthesis, Lange, J., et al., 2012

Glyoxal (amino acids) → Glyoxylate → Oxalate → Urinary Oxalate

Marker for Diabetes and Obesity
Glyoxylate plasma levels
• predict diabetes up to 3 years before diagnosis

Urinary oxalate excretion
• is linked to diabetes independent of dietary oxalate intake
• elevated in both obesity and diabetes from \( \uparrow \) generation and absorption
Diabetes and Obesity = \( \uparrow \) Oxalate in Blood

- Production
- Absorption

\( \downarrow \text{GFR} \)

\( \uparrow \text{Oxalate in Blood} \)

\( \uparrow \text{Oxalate in Tubule} \)

\( \uparrow \text{Tubular Toxicity} \)

\( \uparrow \text{Oxalate / Calcium Obstructions} \)

Hyperoxaluria

Urinary oxalate as a potential mediator of kidney disease in diabetes mellitus and obesity. Efe, O., et al., 2019
HYPEROXALURIA

POOR DIET
1. ULTRA PROCESSED FOOD
2. SUGAR
3. FRUCTOSE - HFCS
4. INDUSTRIAL OILS - PUFAs
5. AGEs - Advanced Glycation End Products

LOW H₂O INTAKE
20% EXCESS DIETARY OXALATES

INTESTINAL DAMAGE
1. INCREASED OXALATE AVAILABILITY
2. DECREASED CALCIUM AVAILABILITY
3. LEAKY GUT
4. ANTIBIOTICs and DRUGs
   a. ORLISTAT
   b. NSAIDs - Non-Steroidal Anti-Inflammatory Drugs

EXTREME OXALATE KIDNEY DAMAGE - 26% with STONES

88% FAT MALABSORPTION

Hydration Biomarkers Are Related to the Differential Abundance of Fecal Microbiota… Willis, N., et al., 2021
20% Dietary Oxalates

88% Intestinal Damage (Fat Malabsorption)

Low Water Intake

Strong Evidence for Low Water Intake

Weak Evidence for Dietary Oxalate Restriction

Diet and Stone Disease in 2022, Dai, J., & Pearle, M., 2022; The Use of Antibiotics and Risk of Kidney Stones, Joshi, S., & Goldfarb, D., 2019
Glyoxal Formation and Its Role in Endogenous Oxalate Synthesis, Lange, J., et al., 2012
Ultra-Processed Food
> 60% of US daily diet

AGEs - Gut
Dysbiosis
Gut inflammation

AGEs - Kidneys
Accumulation
Damage nephron

AGEs - Systemic
Accumulation and Damage in every organ

Role of gut microbiota in the modulation of the health effects of advanced glycation end-products (Review).
Aschner, M., et al., 2023
Antibiotics cause rapid loss of microbial oxalate metabolism

63% elimination of Oxalobacter formigenes after 2-week course

Limited or no recovery of Oxalate metabolism

Strongly linked to risk of kidney stones

70% of CaOx stones contain multi-antibiotic resistant bacteria

Direct antibiotic crystalization of stone formation?
OTHER DRUGS

Drugs that disturb gut bacteria -
- NSAIDs
- osmotic laxatives
- hormones
- benzodiazepines
- antidepressants
- antihistamines
- IBD drugs
- proton pump inhibitors
- metformin
- statins
- psychotropic drugs

> 30 drugs are substrates of gut bacterial enzymes
Oxalate Degrading Network
Oxalate consumption stimulates a wide range of bacteria, which degrade 100% of consumed Oxalate.

Animals receiving N. albigula fecal transplants display similar oxalate-degrading potential for up to 9 months.

N. albigula
Oxalate-degrading bacteria, when present in the GIT tract are able to decrease urine oxalate up to 40% and significant reduction of oxalate stone formation in the kidneys.

Bifidobacterium (B.) spp. and Lactobacillus (L.) spp. have the ability of degradation oxalate into carbon dioxide and formate.
Oxalate degradation has been known since the 1940s but never described.

Focus has been on O. formigenes.

First comprehensive study to characterize oxalate-degrading bacteria in vivo with > 1000 subjects.

The majority (92%) of healthy gut microbiomes include oxalate-degrading enzymes.
Guiding Thoughts
Tragic Oxalate Overdose

Supersaturation
No water

Loss of tolerance
10x legal dose

Utah, 1971

Increased water intake is the universally recognized therapeutic approach for reducing the risk of kidney stones

- 65% adults under-hydrated due to low water intake
- Poor hydration status linked to intestinal inflammation

Water intake to 2 to 3 L per 24 hours
Drink before bed and again during the night
Keep hydrated to prevent fluid loss

Epidemiology of Kidney Stones. Stamatelou, K., & Goldfarb, D., 2023
Nutrition and kidney stone disease. Siener, R., 2021
Hydration Biomarkers Are Related to the Differential Abundance. Willis, N., et al., 2021
Bicarbonate helps eliminate Oxalate

Gerolsteiner Mineral Content mg/L

Bicarbonate 1816
Calcium 384
Magnesium 108

2 L/day of mineral water containing 1715 mg/L bicarbonate significantly increased urine pH and citrate excretion and decreased oxalate excretion

Mineral water bicarbonate determines the risk of stone formation

https://www.gerolsteiner-usa.com/home
Acetic acid 5% reduces KSD risk
5 ml dose 3x/day

60% decreased risk

Chinese study of > 9000 people

Dietary vinegar prevents kidney stone recurrence via epigenetic regulations. Zhu, W., et al., 2019
The gut microbiota consumes oxalate to maintain oxalate homeostasis.

7 strains of Lactobacillus spp. were isolated from dairy products.

These strains showed oxalate-degrading ability plus:
- Ability to tolerate acid, bile salts, and phenol.
- Antibiotic-resistant to a wide range of antibiotics.

Lactobacillus acidophilus and Lactobacillus gasseri, showed significant oxalate degradation activity.
SUPER GUT

A FOUR-WEEK PLAN TO REPROGRAM YOUR MICROBIOME, RESTORE HEALTH, AND LOSE WEIGHT

NATIONAL BESTSELLER

WILLIAM DAVIS, MD

#1 NEW YORK TIMES BESTSELLING AUTHOR OF WHEAT BELLY
Future Developments
Fecal Microbiota Transplant (FMT)
Drug Therapy

Reloxaliase (formerly known as ALLN-177) is a recombinant oxalate decarboxylase

Enzyme used by O. formigenes to degrade oxalate

A randomized trial to be completed in November 2023

Oxadrop is a probiotic composed of Lactobacillus acidophilus, Lactobacillus brevis, Streptococcus thermophilus and Bifidobacterium infantis
Thank you!

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