Casual Friday Series

Metabolic Flexibility: The Overlooked Key Behind Clinical Plateaus

Why patients stall in their weight, energy, detoxification, and hormones

A BIOGENETIX CLINICAL PRESENTATION

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Disclaimer

- *Information in this presentation is not intended, in itself, to diagnose, treat, reverse, cure, or prevent any disease. While this presentation is based on medical literature, findings, and text, The following statements have not been evaluated by the FDA.*
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*

How many times have we seen it?

- Every practitioner sees it… a patient improves, then stalls…
- Weight loss flatlines, energy fizzles, detox slows, hormones stall.
- Why?

Because they are not Metabolically Flexible!

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What is Metabolic Flexibility?

- By Definition… It's the ability to switch between glucose and fat oxidation.
- When Metabolically Flexible = steady ATP → detox, cell repair, cell resilience, and cells are interacting with extra cellular components.
- When Metabolically Inflexible = carb-locked, insulin resistant, fatigued, and cell membranes are "Blunted"

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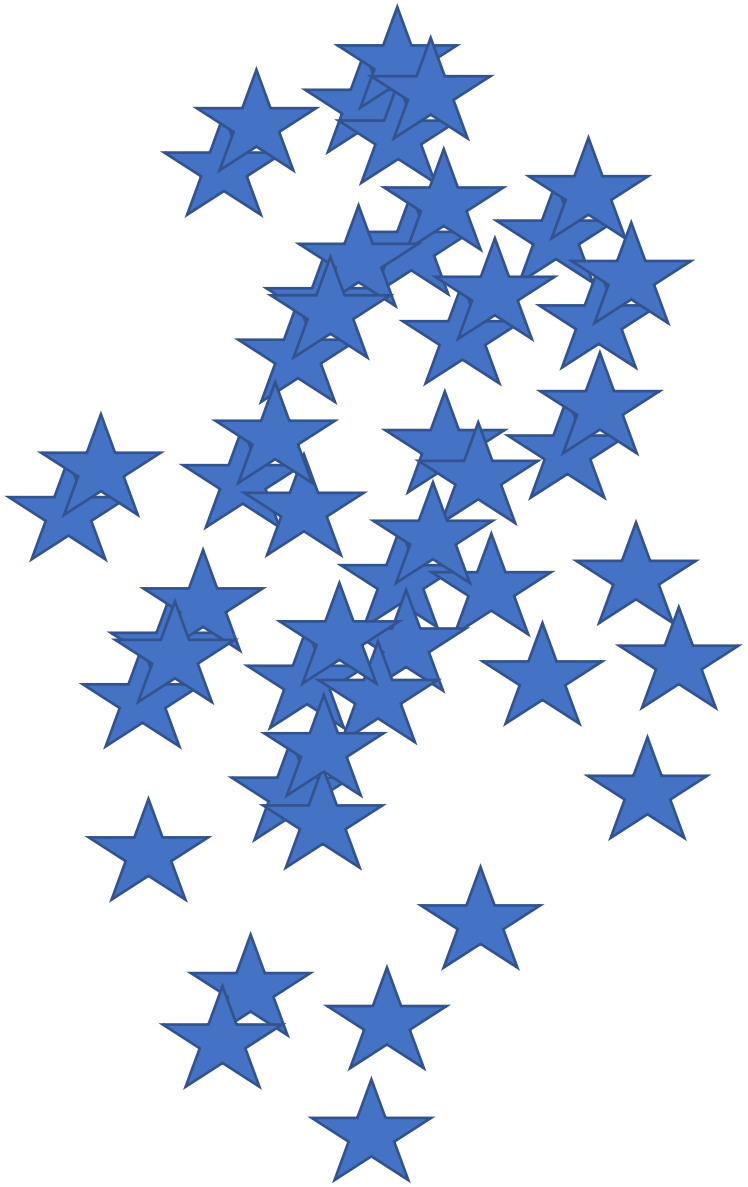
Metabolic flexibility in health and disease

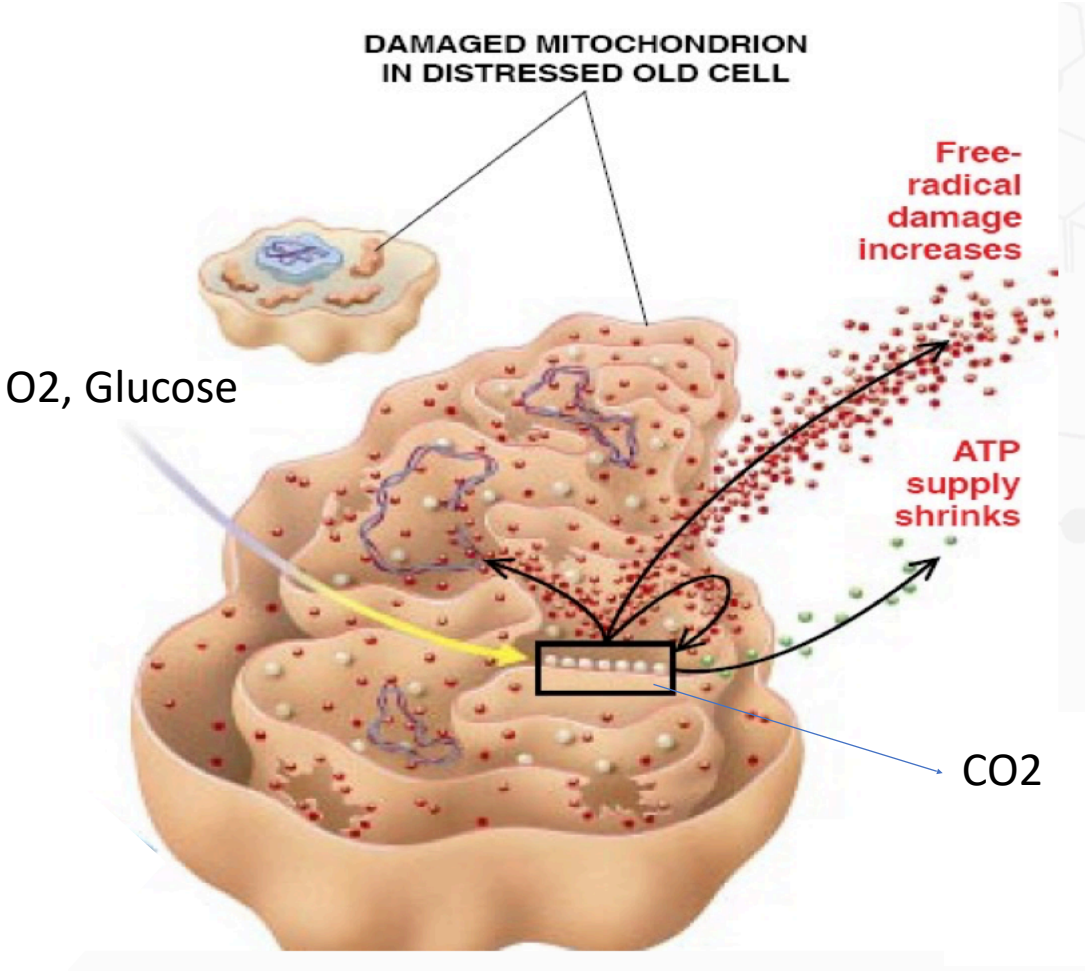
PMCID: PMC5513193 NIHMSID: NIHMS869590 PMID: 28467922

Bret H Goodpaster [1], Lauren M Sparks [1]

Metabolic flexibility is the ability to respond or adapt to conditional changes in metabolic demand. This broad concept has been propagated to explain insulin resistance and mechanisms governing fuel selection between glucose and fatty acids, highlighting the metabolic inflexibility of obesity and type 2 diabetes. In parallel, contemporary exercise physiology research has helped to identify potential mechanisms underlying altered fuel metabolism in obesity and diabetes. Advances in 'omics' technologies have further stimulated additional basic and clinical-translational research to further interrogate mechanisms for improved metabolic flexibility in skeletal muscle and adipose tissue with the goal to prevent and treat metabolic disease.

Kelley et al., 1993). Since those first experiments were described, the term metabolic flexibility has evolved to encompass other metabolic circumstances and tissues and more broadly refers to a physiological adaptability. Metabolic flexibility was also inferred to have tissue specificity in response to nocturnal and diurnal fasted and fed conditions (Kelley et al., 1999).




DAMAGED MITOCHONDRION
IN DISTRESSED OLD CELL
Free-
radical
damage
increases
ATP
supply
shrinks
O2, Glucose
CO2

Why Does Metabolic Flexibility Matter Clinically?

- “All healing requires flexible energy production.”
- Inflexibility = mitochondria stuck → adaptability is lost → progress halts
- This impacts every protocol we can run and applies to: detox, weight loss, energy, and hormones

But how do we spot Metabolic Inflexibility in our clients?

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Spotting Metabolic Inflexibility in Routine Labs (BioG Gen Screen)

- Metabolic flexibility isn't a "mystical" concept — it leaves fingerprints.
- Everyday panels (CBC w Diff, CMP, Lipids, Thyroid, etc) reveal these **rigidity patterns**.
- Don't look for one number — look for **Patterns**.
- *For Example:*
- TG/HDL + insulin = insulin resistance signature
- ALT/AST drift + TG= inflammatory/NAFLD signature

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CBC with Diff

- WBC shifts (High or Low) → hidden inflammation = plateau triggers.
- MCV/MCH → B12/folate deficiency → methylation/ detox stalls.
- RDW → nutrient stress, metabolic rigidity clue.
- Neutrophil/Lymphocyte ratio → chronic stress burden.

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NEUTROPHIL TO LYMPHOCYTE RATIO (NLR) IN PERICARDITIS: A NOVEL MARKER OF INFLAMMATORY RESPONSE

Authors: Alveena Batool Syed, Gauranga Mahalwar, Ashwin Kumar, Sharmeen Sorathia, Zachary S. Yaker, Aqieda Bayat, Ushasi Saraswati, Jaideep Singh Bhalla, Tom Kai Ming Wang, and Allan L. Klein | AUTHORS INFO & AFFILIATIONS

Publication: Journal of the American College of Cardiology • Volume 83, Number 13_Supplement

NLR (neutrophil to lymphocyte ratio) is a marker of inflammatory response and can be used as a diagnostic and prognostic marker in different inflammatory conditions. Elevated levels of hs-CRP and NLR suggest an ongoing inflammatory process. We hypothesize that NLR can be used as a diagnostic inflammatory marker along with other laboratory markers in patients with pericarditis.

Neutrophil-to-lymphocyte ratio as a predictive marker of metabolic syndrome

DOI: 10.1097/MD.0000000000017537

Earlier studies demonstrated an association between increased NLR and decreased overall survival and disease-free survival in melanoma, breast cancer, lung cancer, and gastrointestinal cancer.[12–15]

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Applicability of the Neutrophil/Lymphocyte Ratio in Behavioral Studies

DOI: 10.23937/2469-5696/1410075

The balance of neutrophilic and lymphocytic populations in the body is sensitive to neuroendocrine changes present in acute and chronic emotional stress, influencing a range of behaviors intrinsically related to real or potential environmental stressors. In this sense, the Neutrophil/Lymphocyte Ratio (NLR) is a simple and low-cost tool, derived from the analysis of the blood count, capable of showing changes in several health parameters, since it is related to the pro-inflammatory status of the organism. In this article, through a narrative review of the literature, the applicability of NLR in behavioral studies and its possible clinical uses are presented, both at the diagnostic, prognostic and treatment levels. The physiology of NLR and its relationship with stress, as well as topics such as mental health, obesity, eating behavior, smoking and physical activity are mentioned, NLR appears to be an accurate, useful and promising biomarker for use in monitoring and preventing diseases in health, with an emphasis on mental health. Its study becomes very important for the determination of reference values and understanding of its working mechanisms, which still demands further investigation.

Comprehensive Metabolic Panel

- Glucose alone = soft signal, must pair with insulin.
- ALT/AST (along with TG)→ NAFLD risk, sluggish liver = detox stalls.
- Albumin/Globulin ratio → inflammation vs malnutrition.
- Electrolytes (Na, K, CO_2) → mitochondrial buffering.

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Comprehensive Metabolic Panel

Abnormal liver enzymes: A review for clinicians

- ALT and AST are aminotransferases largely localized in hepatocytes; elevations indicate **hepatocellular stress, damage, or leakage**.
- A liver under chronic inflammatory load (e.g. due to metabolic stress, lipotoxicity, immune activation) → more hepatocyte stress, mitochondrial dysfunction, oxidative damage → higher ALT/AST.
- Over time, hepatocyte dysfunction can reduce **phase I / II detoxification capacity**, impaired glutathione, conjugation, etc. So higher ALT/AST can be a surrogate for lowered “detox reserve.”
- However: ALT/AST are damage *markers*, not direct function measures (i.e. they don’t show how well detox pathways are working).

Kalas MA, Chavez L, Leon M, Taweesedt PT, Surani S. Abnormal liver enzymes: A review for clinicians. World J Hepatol 2021; 13(11): 1688-1698 **PMID: 34904038 DOI: 10.4254/wjh.v13.i11.1688**

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Comprehensive Metabolic Panel

Abnormal liver enzymes: A review for clinicians

- **Albumin** is a negative acute-phase protein: under inflammation, its synthesis declines, and it may undergo greater degradation or redistribution. Thus low albumin often signals systemic inflammation, poor nutrition, or hepatic synthetic compromise.
- **Globulins** (i.e. immunoglobulins, complement, acute phase proteins) rise in inflammation. So the **Albumin/Globulin (A/G or AGR) ratio** compresses two shifts: lower albumin + higher globulins → lower ratio.

Kalas MA, Chavez L, Leon M, Taweesedt PT, Surani S. Abnormal liver enzymes: A review for clinicians. World J Hepatol 2021; 13(11): 1688-1698 **PMID: 34904038 DOI: 10.4254/wjh.v13.i11.1688**

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Comprehensive Metabolic Panel

Mineral requirements for mitochondrial function: A connection to redox balance and cellular differentiation☆

David W. Killilea [a,*], Alison N. Killilea [b]

[a] Office of Research, University of California, San Francisco, CA, USA
[b] Department of Molecular & Cell Biology, University of California, Berkeley, CA, USA

- Eleven of the 12 minerals essential for human health have important roles within mitochondrial metabolism.
- Increased oxidative stress within the mitochondria is a common consequence of aberrant mineral homeostasis.
- Low oxidative stress is key for long-lived cell lineages, so optimizing mineral levels is important for cellular potency.
- Tuning up mineral metabolism should strengthen mitochondrial physiology, and thereby improve cellular health.

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Lipid Panel

- TG/HDL ratio → practical IR marker (>3 = high risk).
- TG/HDL ratio → possible autoimmune or toxicity
- High TG = impaired fat burning, dietary impact
- LDL particle size → oxidative stress, cardiometabolic roadblock. “Clogged drains”

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Inflammation and Methylation

- hs-CRP: systemic inflammation;
  - >3 = high risk of Cardiovascular event
  - ≥10 typically associated with Infection
- Homocysteine: >7 = methylation burden → detox/ vascular stress.

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Inflammation and Methylation

C-Reactive Protein: The Quintessential Marker of Systemic Inflammation in Coronary Artery Disease—Advancing toward Precision Medicine

PMCID: PMC10525787 PMID: 37760885

High-sensitivity C-reactive protein and risk of clinical outcomes in patients with acute heart failure

respectively), as well as a higher risk of recurrent HF admissions ($p < 0.001$). These results remained consistent across important subgroups, such as LVEF, sex, age, or renal function. In patients with acute HF, hsCRP levels were independently associated with an increased risk of long-term death and total HF readmissions.

Santas, E., Villar, S., Palau, P. *et al.* High-sensitivity C-reactive protein and risk of clinical outcomes in patients with acute heart failure. *Sci Rep* **14**, 21672 (2024). https://doi.org/10.1038/s41598-024-72137-0

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Insulin and C-Peptide

- Fasting insulin >6 = hallmark of rigidity.
- C-peptide: pancreas strain vs burnout.
- Can use HOMA-IR for trend tracking.

Vitamin D

- 25-OH D <40 → immune weakness + poor recovery.
- Supports insulin sensitivity in deficient groups.
- Not a panacea, but a modulator.

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Vitamin D's Effect on Immune Function

PMCID: PMC7281985 PMID: 32353972

Ever since its discovery by Windhaus, the importance of the active metabolite of vitamin D (1,25-dihydroxyvitamin D_3; 1,25-(OH)$2D_3$) has been ever expanding. In this review, the attention is shifted towards the importance of the extra-skeletal effects of vitamin D, with special emphasis on the immune system. The first hint of the significant role of vitamin D on the immune system was made by the discovery of the presence of the vitamin D receptor on almost all cells of the immune system. In vitro, the overwhelming effect of supra-physiological doses of vitamin D on the individual components of the immune system is very clear. Despite these promising pre-clinical results, the translation of the in vitro observations to solid clinical effects has mostly failed. Nevertheless, the evidence of a link between vitamin D deficiency and adverse outcomes is overwhelming and clearly points towards avoidance of vitamin D deficiency especially in early life.

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Vitamin D and inflammatory diseases

PMCID: PMC4070857 PMID: 24971027

Beyond its critical function in calcium homeostasis, vitamin D has recently been found to play an important role in the modulation of the immune/inflammation system via regulating the production of inflammatory cytokines and inhibiting the proliferation of proinflammatory cells, both of which are crucial for the pathogenesis of inflammatory diseases. Several studies have associated lower vitamin D status with increased risk and unfavorable outcome of acute infections. Vitamin D supplementation bolsters clinical responses to acute infection. Moreover, chronic inflammatory diseases, such as atherosclerosis-related cardiovascular disease, asthma, inflammatory bowel disease, chronic kidney disease, nonalcoholic fatty liver disease, and others, tend to have lower vitamin D status, which may play a pleiotropic role in the pathogenesis of the diseases. In this article, we review recent epidemiological and interventional studies of vitamin D in various inflammatory diseases. The potential mechanisms of vitamin D in regulating immune/inflammatory responses in inflammatory diseases are also discussed.

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Thyroid Panel

- TSH, Total T3/T4 + free T3/T4 = metabolic throttle or brakes.
- Reverse T3 = stress lock on metabolism.
- Poor conversion = classic plateau pattern. Need to look into the gut and liver.

Iron Panel

- High ferritin = acute inflammatory block, IR link.
- Low ferritin = oxygen delivery limit → fatigue. Life blood of the body (pun intended)

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Effect of iron supplementation on fatigue in nonanemic menstruating women with low ferritin: a randomized controlled trial

PMID: 22777991 PMCID: PMC3414597 DOI: 10.1503/cmaj.110950

Background: The true benefit of iron supplementation for nonanemic menstruating women with fatigue is unknown. We studied the effect of oral iron therapy on fatigue and quality of life, as well as on hemoglobin, ferritin and soluble transferrin receptor levels, in nonanemic iron-deficient women with unexplained fatigue.

Interpretation: Iron supplementation should be considered for women with unexplained fatigue who have ferritin levels below 50 µg/L. We suggest assessing the efficiency using blood markers after six weeks of treatment. Trial registration no. EudraCT 2006-000478-56.

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Why cells need iron: a compendium of iron utilisation

https://doi.org/10.1016/j.tem.2024.04.015

Megan R. Teh [1], Andrew E. Armitage [1], Hal Drakesmith [1]

- Iron has a key role in multiple important cellular processes, including gene regulation, metabolism, bioenergetics, and hormone synthesis.
- Iron deficiency is globally widespread and associated with several and diverse impacts on health, the underlying mechanisms of which are poorly understood.
- We describe potential molecular causative links between cellular iron deficiency and a range of symptoms, and indicate important unknowns in the field.

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Pattern Recognition is the Key

- Start to understand and look for the patterns, not single numbers.
- All progress needs flexible mitochondria.
- Once locked in one mode, Metabolic Flexibility aka Adaptability is lost.

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Pattern Recognition is the Key: Examples

Metabolic Rigidity:
- TG/HDL ratio >2.0
- Fasting insulin >6 µIU/mL
- hs-CRP >1.0 mg/L (risk climbs >3.0)

Mitochondrial Fatigue:
- Vitamin D <50 ng/mL
- Ferritin: M 50–100 ng/mL | F 40–80 ng/mL
- TSH >2.5 mIU/L or Free T3 <3 pg/mL

Detox Stall:
- MCV >92 fL
- RDW >13.5%
- Homocysteine >7 µmol/L
- ALT >25 U/L (men) | >22 U/L (women)

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Pattern Recognition is the Key: Examples

Inflammatory / Malnutrition:
- Albumin/Globulin ratio <1.5
- CRP >1.0 mg/L
- Ferritin >100 (M) | >80 (F)

Buffering / Wiring Strain:
- Potassium <4 mmol/L
- Sodium >140 mmol/L
- CO_2 <25 mmol/L

Stress Lock:
- NLR >2.0
- Reverse T3 >18 ng/dL
- Insulin >6 µIU/mL

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Hypothalamic inflammation: a double-edged sword to nutritional diseases

PMCID: PMC4389774 NIHMSID: NIHMS667069 PMID: 22417140

Diurnal Cortisol Slopes and Mental and Physical Health Outcomes:A Systematic Review and Meta-analysis

PMCID: PMC5568897 NIHMSID: NIHMS881368 PMID: 28578301

Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk

PMCID: PMC3341031 PMID: 22474371

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Restoring Metabolic Flexibility

Lifestyle Considerations

Diet Variation:

- **Protein first**
- **Smart fats:** olive oil, avocados, etc
- **2–3 meals, no grazing:** 4–5h between meals; small protein-only snack only if needed
- **“Feast” Days:** designate at least one day a week for more healthy/approved carbs
- **Hydration/electrolytes:** Half body weight in ounces of water; include a quality salt especially am and noon.
- **Short fasts:** 12–14h most days; option advanced protocols as they become more flexible

Circadian alignment: Morning outdoor light, fixed sleep/wake, last meal ≥3h before bed, no blue light before bed

Move often: 10-min walk after meals, 2–3× resistance, Interval training

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Restoring Metabolic Flexibility

Nutritional Support Considerations - Remember that it is important and essential to continue to look for the “roots” and to identify any physiology weakness specific to each client.

HPA / Stress Rhythm

- **Hypaax Balance** — adaptogenic HPA support
- **P/S Support** — phospholipid support for healthy cortisol rhythm & mood
- **BioG-Max GABA** — calm parasympathetic support

Insulin Sensitivity / TG:HDL

- **Berberine X** — for glucose & lipids; take with meals.
- **Glucostatic Balance** — for insulin receptor site sensitivity.
- **Effecsulin** — for post-prandial control on higher-carb days.
- **Omega-3 Softgels** — supports glucose/insulin metabolism + pro-resolving mediators.

Inflammation Tone / Gut Barrier

- **Kapp-X** — NF-κB-targeted botanical blend
- **GI ResQ+** — for mucosal repair.
- **UltraBiotix** — probiotic

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Restoring Metabolic Flexibility

Nutritional Support Considerations - Remember that it is important and essential to continue to look for the “roots” and to identify any physiology weakness specific to each client.

Vitamin D / Immune & Metabolic Modulation

- **D3K2 Capsules or Liquid** — D3 with MK-7 K2; immune, cardio-metabolic, and insulin-signaling support; retest 25-OH D in 8–12 wks. (Biogenetix)

Detox / Liver (ALT/AST patterns)

- **21-Day Metabolic Clearing Program Hepato-CL** — Liver detox support; pair during reintroduction phase.
- **Pure NAC** + **BioG-Max GSH** — Glutathione synthesis + direct GSH delivery.
- **BioG-Max C w/ R-Lipoic** — Antioxidant support

Mitochondrial Capacity / Energy

- **BioG-Max CoQ10** — electron transport chain support
- **BioG-Max NAD+** — cellular bioenergetics/ATP resilience; pairs well with clearing program.
- **BioG-Max PC** — membrane/mitochondrial & bile support.

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Restoring Metabolic Flexibility

Nutritional Support Considerations - Remember that it is important and essential to continue to look for the “roots” and to identify any physiology weakness specific to each client.

Meals / Digestion (Diet Variation days)

- **Zymetix —** broad-spectrum enzymes for protein/fat/carb/fiber on “feast” or dining-out days.

Baseline Micros / Electrolytes

- **Multi+ Powder or BioG-Max Multi+ —** activated B-complex, chelated minerals, 5-MTHF, methyl-B12, TMG (methylation)
- **Quality salt** particularly in the AM and noon

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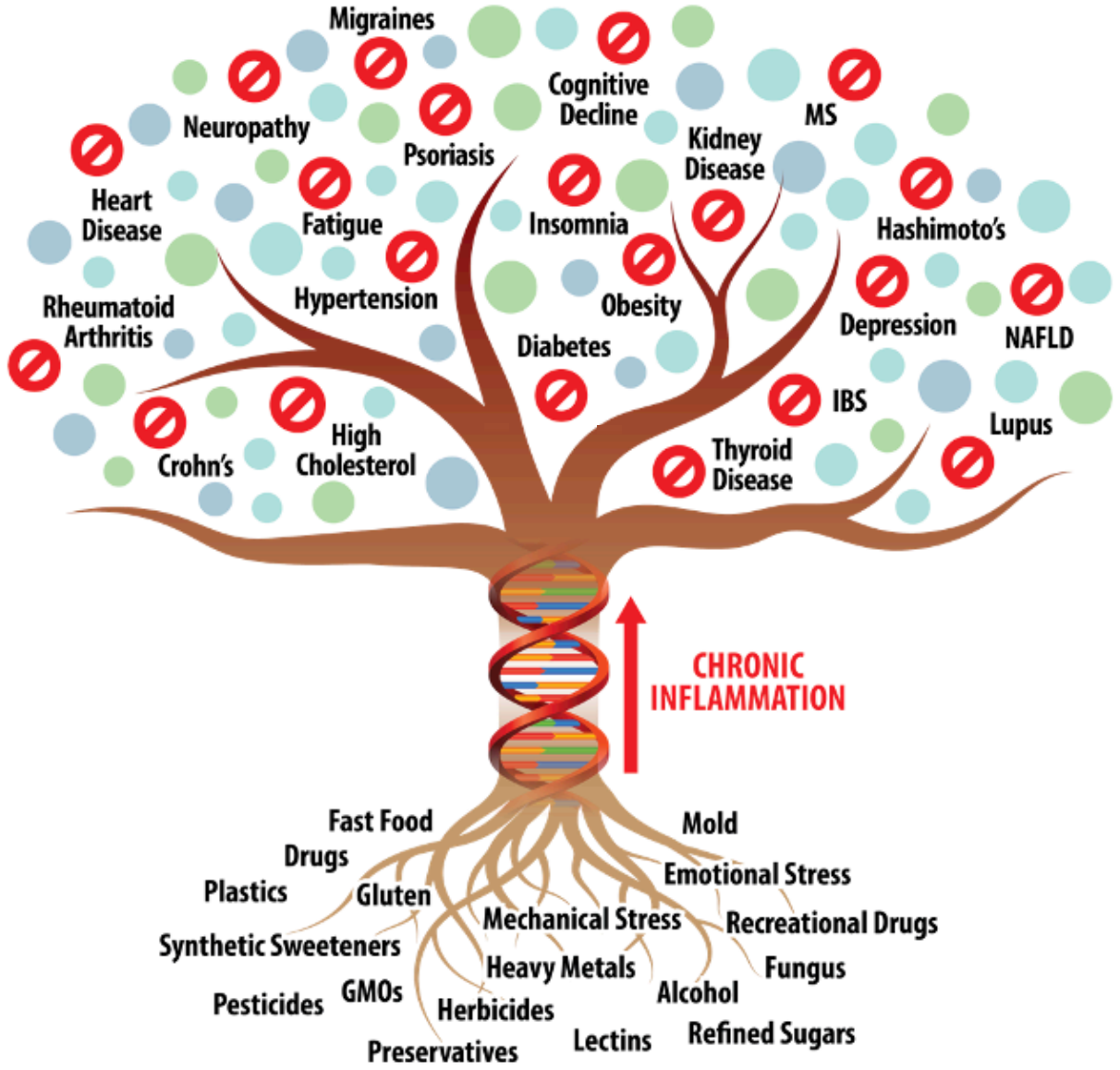
Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Drugs
Plastics
Gluten
Mold
Emotional Stress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

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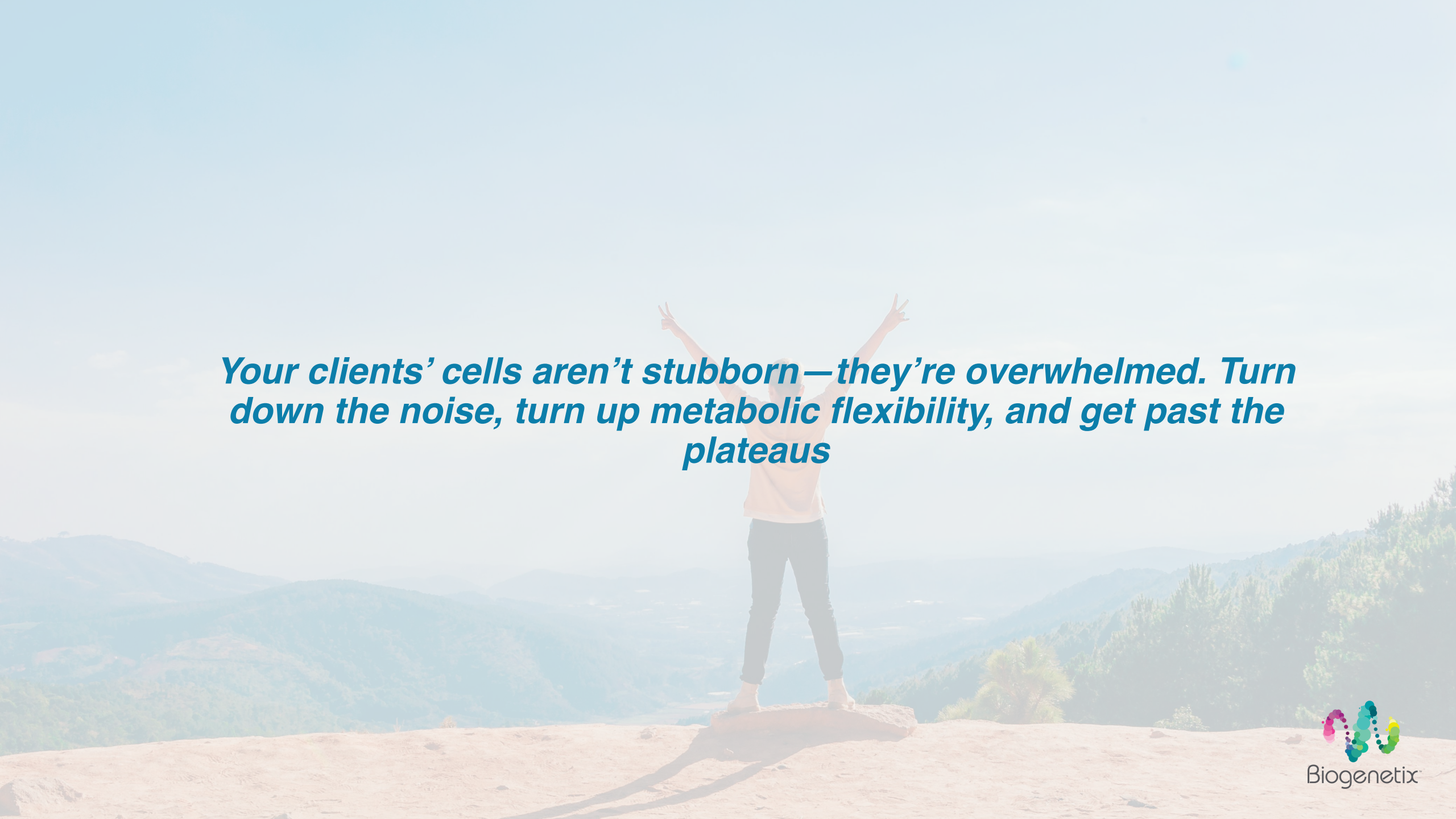

Your clients' cells aren't stubborn—they're overwhelmed. Turn down the noise, turn up metabolic flexibility, and get past the plateaus

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