FUNCTIONAL MEDICINE
Continuing Education

“Complete” Mental Health Laboratory Assessment

Carrie Jones, ND, MPH, FABNE

Disclosures:

- Head of Medical Education at Rupa Health
- SOS Stress Expert Consultant at the Lifestyle Matrix Resource Center (LMRC)

Objectives:

To review and understand common and advanced lab work as it relates to:

1. Inflammation, depression and anxiety: glucose, insulin, hs CRP, IL-6, ferritin, and more
2. Hormonal testing, depression and anxiety: Estradiol, progesterone, testosterone, thyroid and cortisol
3. Microbiome testing, depression and anxiety: bacteria/LPS, zonulin, sIgA, calprotectin, candida, parasites, and more

First and foremost:

Depression is multi-faceted. There are several reasons for depression that simply can't be tested for such as trauma.

However, there are several reasons for depression that have been known for decades and can be tested, yet little has been done to address it other than "Here, try this anti-depressant" or "Here, try this anti-anxiety."

There isn't enough time to cover all the possible reasons for depression that can be tested, but **this webinar serves as a start.**

Inflammation

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International Journal of Neuropsychopharmacology (2002), **5**, 401–412. Copyright © 2002 CINP
DOI: 10.1017/S1461145702003164

Effects of antidepressants on the production of cytokines

Gunter Kenis and Michael Maes

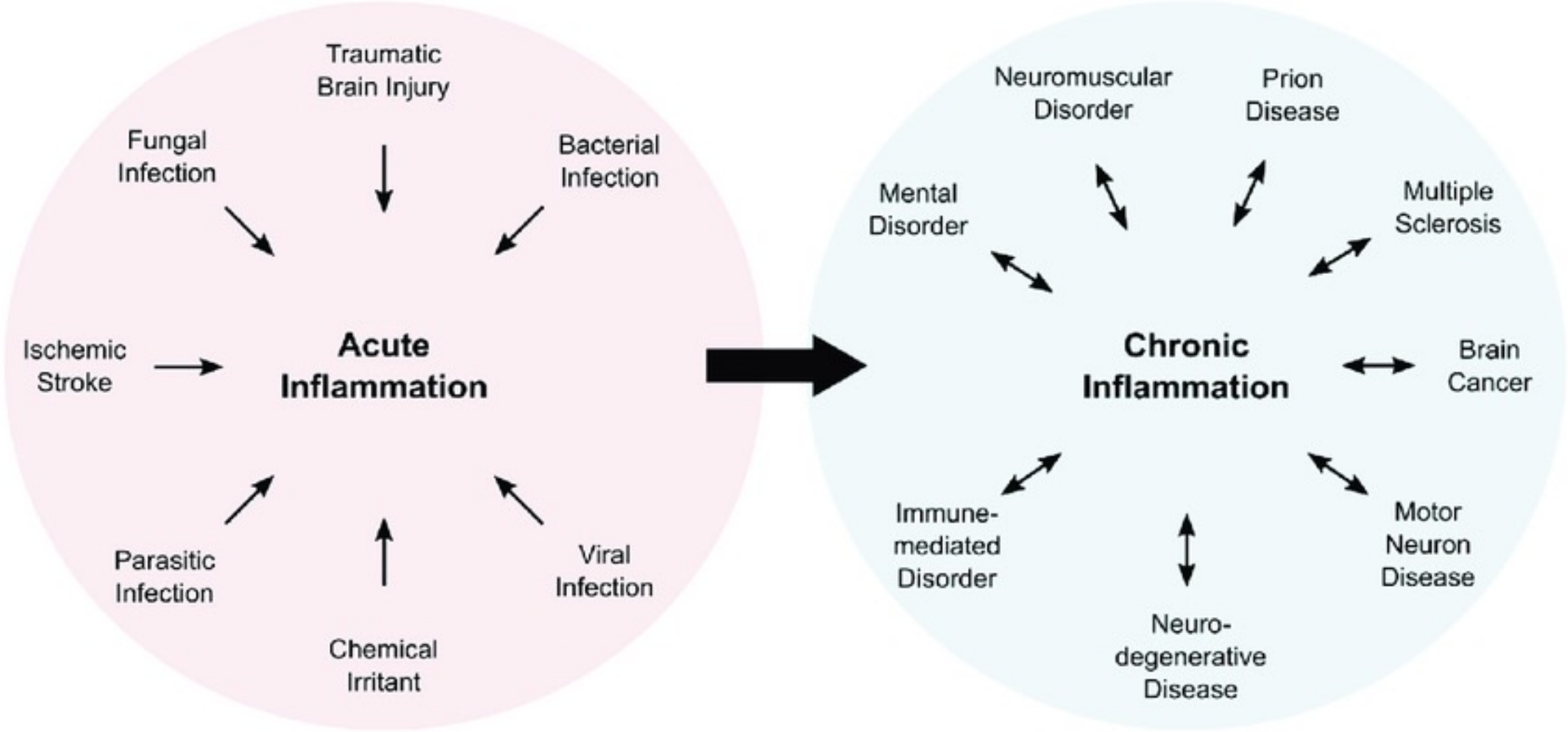
Department of Psychiatry and Neuropsychology, University of Maastricht, Maastricht, The Netherlands

Abstract

There is now evidence that major depression is associated with an up-regulation of the inflammatory response system (IRS). One of the major factors in this IRS activation is the hyperproduction of pro-inflammatory cytokines. Recently, a number of studies examined whether there is a causative role of these inflammatory mediators in the aetiology of major depression. Studies with animal models and cytokine immune therapy in humans suggest that pro-inflammatory cytokines induce depressive symptomatology. Moreover, these depressive symptoms can be effectively reversed by antidepressant treatment. Thus, it may be suggested that antidepressants suppress pro-inflammatory cytokine production and/or action, resulting in improvement of depressive symptoms. The influence of antidepressants on cytokine production has been examined in culture systems in vitro, and in animal models of depression – in which cytokine production is induced by endotoxin administration. Results suggest that antidepressants of several classes decrease the production of pro-inflammatory cytokines such as interferon-γ and tumour necrosis factor-α, and increase that of interleukin-10, an anti-inflammatory cytokine. Further, the effect of antidepressive treatment on cytokine secretion and on plasma levels of cytokines in depressed patients has been studied. Unfortunately, different approaches to examine cytokine production and different techniques to measure cytokines in plasma are used in these studies. Despite this, current data indicate a normalization of cytokine plasma levels and cytokine production after antidepressant treatment. It is clear, however, that more research is warranted and we strongly argue the need for higher standardization in the methodology used to examine the cytokine network in depressed patients.

“**Depression has been associated with inflammatory markers since 1985**. Reduced numbers of red blood cells, hematocrit and hemoglobin, and increased reticulocyte number and changes in iron metabolism that are consistent with the inflammatory process have been observed in individuals presenting with major depressive illness. These observations are comparable with already established markers of inflammation (reduced levels of serum albumin and zinc) that are present during episodes of depression.”

Farooq RK, Asghar K, Kanwal S, Zulqernain A. Role of inflammatory cytokines in depression: Focus on interleukin-1β . Biomed Rep.2017; 6(1):15-20.



Fernandes EFA, Özcelik D. Imaging Biomarkers for Monitoring the Inflammatory Redox Landscape in the Brain Antioxidants. 2021; 10(4):528-.

Markers to consider:

- Inflammatory cytokines
- Fasting insulin, glucose and hemoglobin A1c
- Fibrinogen
- hsCRP
- Complete blood count
- Comprehensive metabolic panel
- Ferritin, iron, TIBC
- Zinc

Interleukin-6 (IL-6)

- **Major pro-inflammatory cytokine**
- Serum levels shown higher in depressed pts compared to non-depressed pts
- Antidepressants appear to lower proinflammatory cytokines
  - Non-responders to antidepressants appear to still have elevated levels

- Farooq RK, Asghar K, Kanwal S, Zulqernain A. Role of inflammatory cytokines in depression: Focus on interleukin-1β. Biomed Rep. 2017; 6(1):15-20. [PDF]
- Kenis G, Maes M. Effects of antidepressants on the production of cytokines Int. J. Neuropsychopharm.. 2002; 5(4):401-412.

Glucose Levels

Proposed Optimal Glucose Ranges

Value	Levels team optimal goal	Standard range for normal
Fasting glucose	72-85 mg/dL	< 100 mg/dL
Pre-meal (baseline glucose)	72-90 mg/dL	72-90 mg/dL
Post-meal glucose peak	<110 mg/dL, with <30 mg/dL increase from pre-meal levels	< 140 mg/dL
Mean 24-hour glucose	79-100 mg/dL	89-104 mg/dL
Recommended in-app range	72-110 mg/dL	70-140 mg/dL

https://www.levelshealth.com/blog/what-should-my-glucose-levels-be-ultimate-guide

Fasting Glucose Goal: 72-85 Mg/dL

Why? Previously we discussed that the ADA considers normal fasting glucose as anything <100 mg/dl. However, multiple research studies show that as fasting glucose increases, there is an increased risk of health problems like diabetes and heart disease — even if it stays within the normal range. The highlights of some of the study results include:

- Men whose fasting blood glucose was greater than 85 mg/dl had a significantly higher mortality rate from cardiovascular diseases than men with blood sugars less than 85 mg/dl. (Bjornholt et al.)
- People with fasting glucose levels in the high normal range (95-99 mg/dl) had significantly increased cardiovascular disease risk than people whose levels remained below 80 mg/dl. (Park et al.)
- Children with fasting glucose levels 86-99 mg/dl had more than double the risk of developing prediabetes and Type 2 diabetes as adults when compared with children whose levels were less than 86 mg/dl. (Nguyen et al.)
- People with fasting glucose levels between 91-99 mg/dl had a 3-fold increase in Type 2 diabetes risk compared to those with levels less than 83 mg/dl. (Brambilla et al.)
- Among young, healthy men, higher fasting plasma glucose levels within the normal range constitute an independent risk factor for Type 2 diabetes. This means that as fasting glucose increases, even if the level is still considered "normal," it could indicate a significantly higher risk of developing diabetes, and this is particularly pronounced if BMI is greater than 30. (Tirosh, et al.).

https://www.levelshealth.com/blog/what-should-my-glucose-levels-be-ultimate-guide

Hemoglobin A1c

- Glycated hemoglobin (attached to a sugar)
- Represents an avg blood sugar over time
- The American Diabetes Association says:

Result	A1C
Normal	less than 5.7%
Prediabetes	5.7% to 6.4%
Diabetes	6.5% or higher

https://www.diabetes.org/diabetes/a1c/diagnosis

Hemoglobin A1c

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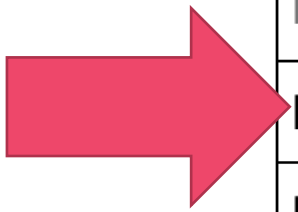

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Normal	less than 5.7%
Prediabetes	5.7% to 6.4%
Diabetes	6.5% or higher

https://www.diabetes.org/diabetes/a1c/diagnosis

HbA1c %	eAG mg/dL	HbA1c %	eAG mg/dL	HbA1c %	eAG mg/dL
5	97	7	154	10	240
5.2	103	7.2	160	10.2	246
5.4	108	7.4	166	10.4	252
5.6	114	7.6	171	10.6	258
5.8	120	7.8	177	10.8	263
6	126	8	183	11	269
6.2	131	8.2	189	11.2	275
6.4	137	8.4	194	11.4	280
6.6	143	8.6	200	11.6	286
6.8	148	8.8	206	11.8	292
		9	212	12	298
		9.2	217		
		9.4	223		
		9.6	229		
		9.8	235		

https://www.hcp.jentadueto.com/resources/practice

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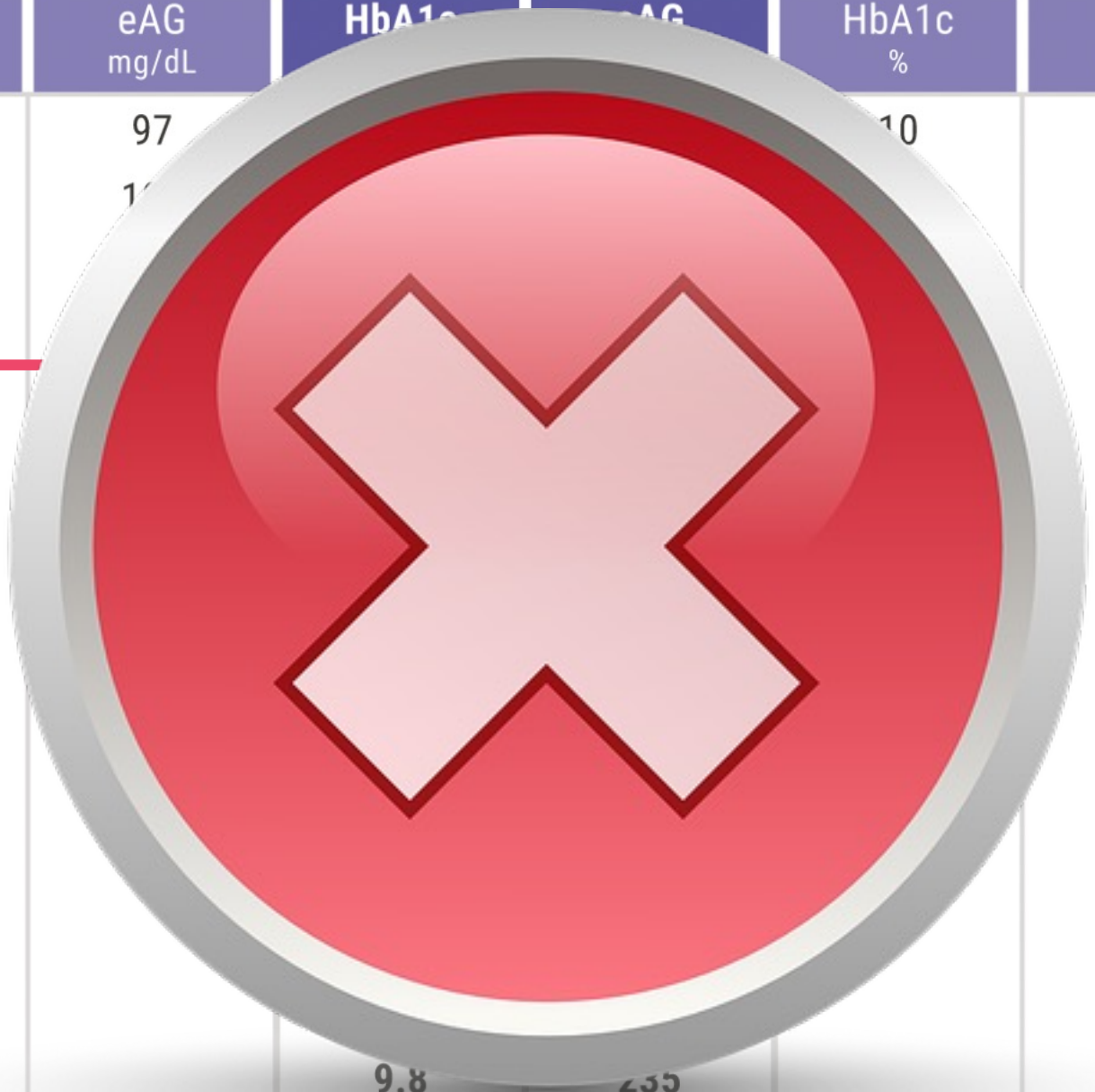

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https://www.hcp.jentadueto.com/resources/practice

Insulin Levels

Insulin level	Insulin level (SI units*)
Fasting	<25 mIU/L

- https://www.medicinenet.com/what_is_a_high_insulin_level/article.htm
- Chen, Y. H., Lee, Y. C., Tsao, Y. C., Lu, M. C., Chuang, H. H., Yeh, W. C., Tzeng, I. S., & Chen, J. Y. (2018). Association between high-fasting insulin levels and metabolic syndrome in non-diabetic middle-aged and elderly populations: a community-based study in Taiwan. *BMJ open*, *8*(5), e016554. https://doi.org/10.1136/bmjopen-2017-016554
- Johnson JL, Duick DS, Chui MA, et al. . Identifying prediabetes using fasting insulin levels. *Endocr Pract* 2010;16:47–52. 10.4158/EP09031.OR

Insulin Levels

Insulin level	Insulin level (SI units*)
Fasting	<25 mIU/L

Functional recommendations vary.

I have seen:

- 2-5 mIU/L
- <7mIU/L
- <9mIU/L

- https://www.medicinenet.com/what_is_a_high_insulin_level/article.htm
- Chen, Y. H., Lee, Y. C., Tsao, Y. C., Lu, M. C., Chuang, H. H., Yeh, W. C., Tzeng, I. S., & Chen, J. Y. (2018). Association between high-fasting insulin levels and metabolic syndrome in non-diabetic middle-aged and elderly populations: a community-based study in Taiwan. *BMJ open*, *8*(5), e016554. https://doi.org/10.1136/bmjopen-2017-016554
- Johnson JL, Duick DS, Chui MA, et al. . Identifying prediabetes using fasting insulin levels. *Endocr Pract* 2010;16:47–52. 10.4158/EP09031.OR

Why a fasting ”low” insulin?

- “After adjusting for gender, age, BMI, smoking status, hypertension and dyslipidaemia, the middle-aged and elderly populations in the high FI group were at significant risk for developing MetS (OR=5.04, 95% CI=2.15 to 11.81; P<0.01). This conclusion is consistent with previous findings.”
- In this study, **high fasting insulin of n=104 was >7.9**
  - Moderate fasting insulin levels were 4.9-7.8

Chen, Y. H., Lee, Y. C., Tsao, Y. C., Lu, M. C., Chuang, H. H., Yeh, W. C., Tzeng, I. S., & Chen, J. Y. (2018). Association between high-fasting insulin levels and metabolic syndrome in non-diabetic middle-aged and elderly populations: a community-based study in Taiwan. *BMJ open*, *8*(5), e016554. https://doi.org/10.1136/bmjopen-2017-016554

Fibrinogen (Factor I)

- Glycoprotein complex made in the liver
- Broken down to fibrin → fibrin-based blood clot
- Levels increase with **systemic inflammation** and/or tissue damage or injury, infection, etc.
    - Considered an acute phase reactant

Range: Adult: 200-400 mg/dL

https://emedicine.medscape.com/article/2085501-overview#a2

Psychoneuroendocrinology. 2013 May;38(5):638-47. doi: 10.1016/j.psyneuen.2012.08.006. Epub 2012 Sep 14.

Elevated plasma fibrinogen, psychological distress, antidepressant use, and hospitalization with depression: two large population-based studies

Marie Kim Wium-Andersen [1], David Dynnes Ørsted, Børge Grønne Nordestgaard

Affiliations + expand

PMID: 22981529 DOI: 10.1016/j.psyneuen.2012.08.006

Conclusion: Elevated levels of fibrinogen were associated with psychological distress, use of antidepressant medication, and with hospitalization with depression in 73,367 individuals from the general population, in cross-sectional studies and in prospective studies for hospitalization with depression.

Abstract

Objectives: Low-grade systemic inflammation may contribute to the development of depression. We tested the hypothesis that elevated plasma levels of the inflammatory marker fibrinogen are associated with psychological distress, use of antidepressant medication, and with hospitalization with depression in the general population.

Methods: We examined 73,367 20-100 year old men and women from two large population-based studies, the Copenhagen General Population Study and the Copenhagen City Heart Study. We measured plasma fibrinogen and recorded symptoms of psychological distress, use of antidepressant medication, and hospitalization with depression in both cross-sectional and prospective studies.

Results: In cross-sectional analyses, a stepwise increase in fibrinogen percentile categories was associated with a stepwise increase in risk of psychological distress, use of antidepressant medication, and hospitalization with depression (p-trend 2×10(-11) to 5×10(-95)). Furthermore, when different classes of antidepressant medication were examined, a stepwise increase in fibrinogen percentile categories was associated with a stepwise increase in risk of use of Selective Serotonin Reuptake Inhibitors and Tricyclic Antidepressants (p-trend 7×10(-18) and 6×10(-7),

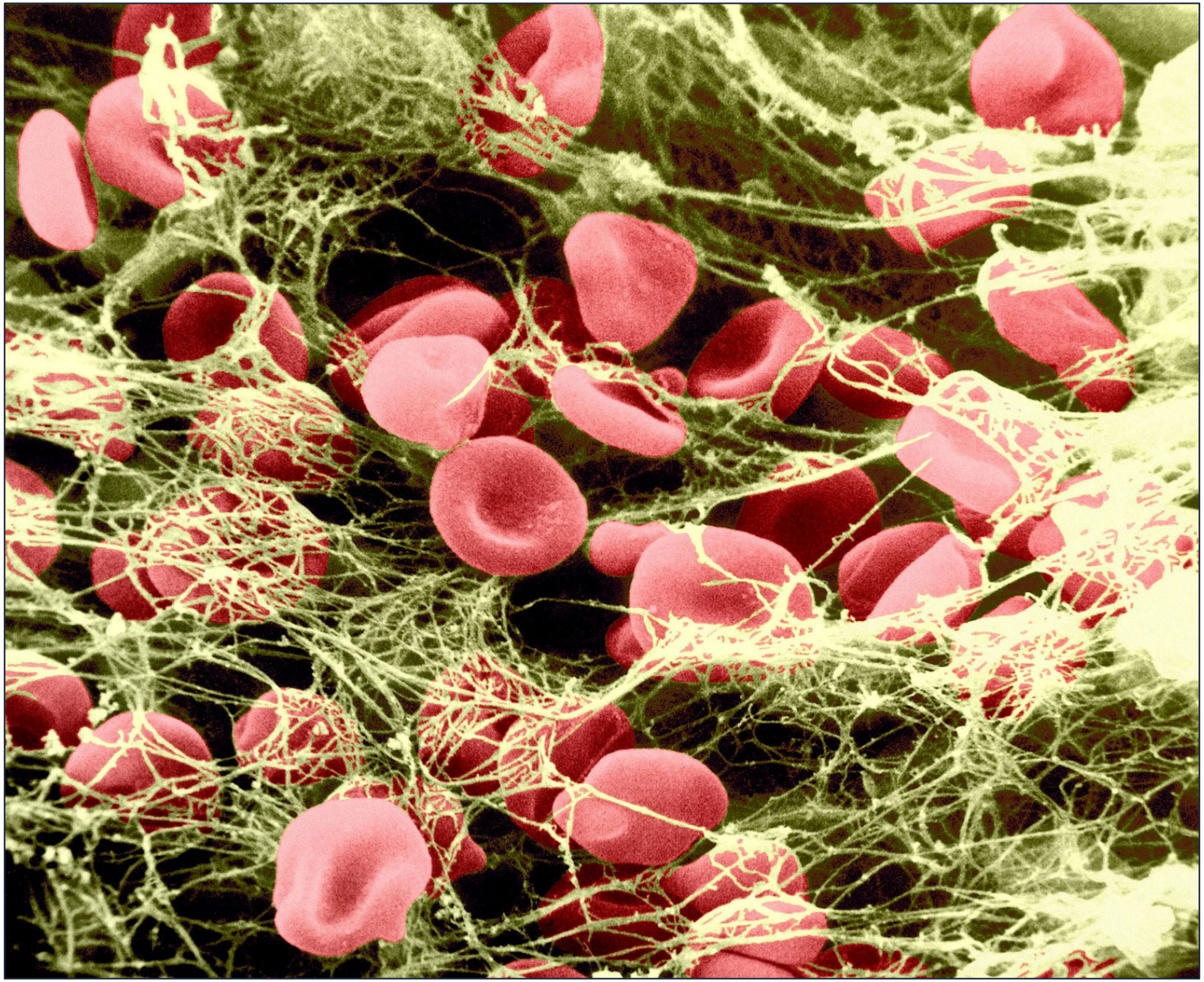

Photo: https://www.britannica.com/science/fibrin

High sensitivity C-reactive protein (hs-CRP)

- Glycoprotein made in the liver
- Increases with **inflammation** and tissue damage
  - Acute phase reactant = rises within about 6 hours
  - **Further stimulates inflammatory cytokines**
  - Inhibits insulin binding in muscles = worsening insulin resistance
- The ‘hs’ = **vascular inflammation**
- Elevated levels = increased risk of coronary events, stroke, peripheral vascular disease, and type 2 diabetes mellitus

Hribal ML, Fiorentino TV, Sesti G. Role of C reactive protein (CRP) in leptin resistance. *Curr Pharm Des*. 2014;20(4):609-615. doi:10.2174/13816128113199990016

International Journal of
Molecular Sciences

MDPI

Review

C-Reactive Protein as a Biomarker for Major Depressive Disorder?

Laura Orsolini, Simone Pompili, Silvia Tempia Valenta, Virginio Salvi and Umberto Volpe *

Unit of Clinical Psychiatry, Department of Neurosciences/DIMSC, Polytechnic University of Marche, 60126 Ancona, Italy; l.orsolini@staff.univpm.it (L.O.); smn.pmpl@gmail.com (S.P.); silvia.tempia@gmail.com (S.T.V.); v.salvi@staff.univpm.it (V.S.)
* Correspondence: u.volpe@staff.univpm.it

Abstract: The etiopathogenesis of depression is not entirely understood. Several studies have investigated the role of inflammation in major depressive disorder. The present work aims to review the literature on the association between C-Reactive Protein (CRP) and depression. A systematic review was performed for the topics of 'CRP' and 'depression' using the PubMed database from inception to December 2021. Fifty-six studies were identified and included in the review. Evidence suggested the presence of dysregulation in the inflammation system in individuals with depression. In most studies, higher blood CRP levels were associated with greater symptom severity, a specific pattern of depressive symptoms, and a worse response to treatment. Moreover, about one-third of depressed patients showed a low-grade inflammatory state, suggesting the presence of a different major depressive disorder (MDD) subgroup with a distinct etiopathogenesis, clinical course, treatment response, and prognosis, which could benefit from monitoring of CRP levels and might potentially respond to anti-inflammatory treatments. This work provides robust evidence about the potential role of CRP and its blood levels in depressive disorders. These findings can be relevant to developing new therapeutic strategies and better understanding if CRP may be considered a valuable biomarker for depression.

hs-CRP Value	Cardiovascular Disease Risk Level*
< 1 mg/L	**low** risk
1-3 mg/L	**average** risk
> 3 mg/L	**high** risk

* Risk levels published in 2003. American Heart Association / Centers for Disease Control and Prevention Scientific Statement

http://www.medical-labs.net/c-reactive-protein-crp-hs-crp-1438/

Iron and Mood?

Psychiatric disorders risk in patients with iron deficiency anemia and association with iron supplementation medications: a nationwide database analysis

Herng-Sheng Lee, Hsin-Hao Chao, Wan-Ting Huang, Solomon Chih-Cheng Chen & Hsin-Yi Yang

BMC Psychiatry **20**, Article number: 216 (2020) | Cite this article

Abstract

Background

It has been shown that iron deficiency anemia (IDA) is associated with psychosocial consequences and psychiatric morbidity. However, the association between adults with IDA and psychiatric disorders has not been clarified. The purpose of this study was to investigate the psychiatric disorder morbidity of an IDA group in comparison with a non-IDA group and to examine the risk of psychiatric disorders in IDA patients treated with iron supplementation

Results

The adjusted hazard ratios (aHRs) of psychiatric disorders was 1.52 (95% CI = 1.45–1.59) in the IDA group compared with the non-IDA group. Among the different types of psychiatric disorders, the IDA group was associated with significantly higher incidence and risks of anxiety disorders, depression, sleep disorders, and psychotic disorders ($p < 0.05$). Furthermore, iron supplementation in IDA subjects was associated with a significantly lower risk of psychiatric disorders compared to non-iron supplementation in IDA patients.

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Published in final edited form as:
Annu Rev Nutr. 2010 Aug 21; 30: 105–122.
doi: 10.1146/annurev.nutr.012809.104804

PMCID: PMC3108097
NIHMSID: NIHMS294977
PMID: 20420524

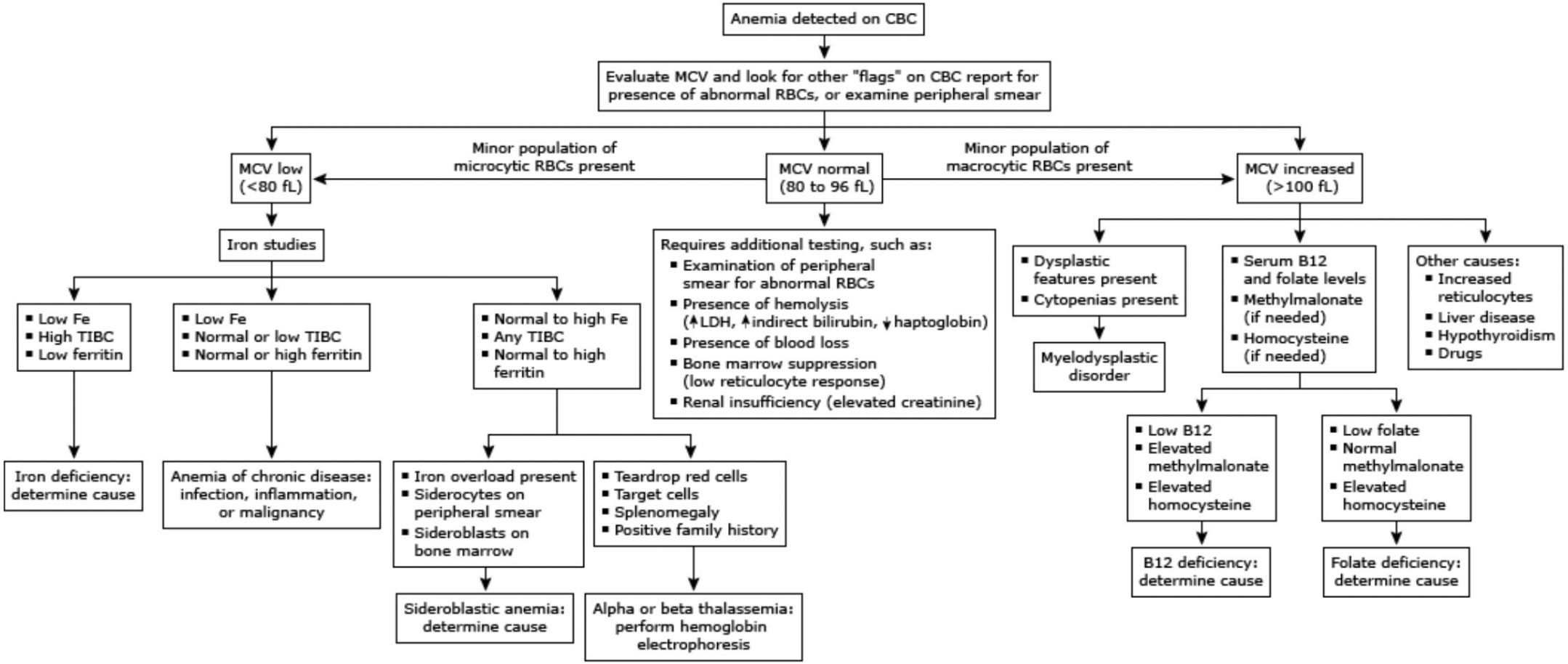
Iron Homeostasis and the Inflammatory Response

Marianne Wessling-Resnick*

Abstract

Go to:

Iron and its homeostasis are intimately tied to the inflammatory response. The adaptation to iron deficiency, which confers resistance to infection and improves the inflammatory condition, underlies what is probably the most obvious link: the anemia of inflammation or chronic disease. A large number of stimulatory inputs must be integrated to tightly control iron homeostasis during the inflammatory response. In order to understand the pathways of iron trafficking and how they are regulated, this chapter will present a brief overview of iron homeostasis. A major focus will be on the regulation of the peptide hormone hepcidin during the inflammatory response and how its function contributes to the process of iron withdrawal. The review will also summarize new and emerging information about other iron metabolic regulators and effectors that contribute to the inflammatory response. Potential benefits of treatment to ameliorate the hypoferremic condition promoted by inflammation will also be considered.



Uptodate.com. (2022). *Evaluation of anemia in the adult*. [online] Available at: http://www.uptodate.com/contents/image?imageKey=HEME/99491&topicKey=HEME%2F7133&source=outline_link&search=anemia+work-up&selectedTitle=1~150&utdPopup=true

Ferritin: Acute Phase Reactant?

Int Immunol. 2017 Nov; 29(9): 401–409.
Published online 2017 May 25. doi: 10.1093/intimm/dxx031
PMCID: PMC5890889
PMID: 28541437

Hyperferritinemia and inflammation

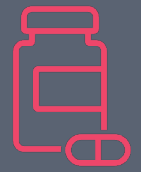
Kate F Kernan[1, 2] and Joseph A Carcillo[1, 2]

Abstract

Go to:

Understanding of ferritin biology has traditionally centered on its role in iron storage and homeostasis, with low ferritin levels indicative of deficiency and high levels indicative of primary or secondary hemochromatosis. However, further work has shown that iron, redox biology and inflammation are inexorably linked. During infection, increased ferritin levels represent an important host defense mechanism that deprives bacterial growth of iron and protects immune cell function. It may also be protective, limiting the production of free radicals and mediating immunomodulation. Additionally, hyperferritinemia is a key acute-phase reactants, used by clinicians as an indication for therapeutic intervention, aimed at controlling inflammation in high-risk patients. One school of thought maintains that hyperferritinemia is an 'innocent bystander' biomarker of uncontrolled inflammation that can be used to gauge effectiveness of intervention. Other schools of thought maintain that ferritin induction could be a protective negative regulatory loop. Others maintain that ferritin is a key mediator of immune dysregulation, especially in extreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects. There is a clear need for further investigation of the role of ferritin in uncontrolled inflammatory conditions both as a biomarker and mediator of disease because its occurrence identifies patients with high mortality risk and its resolution predicts their improved survival.

Nutrients



Zinc

- Essential trace mineral
- “The regulatory functions of zinc ions, together with their functions as a cofactor in about three thousand zinc metalloproteins, impact virtually all aspects of cell biology.” (Maret, 2017)
- **Deficiency due to:**
  - Not eating it
  - Not absorbing it
  - Increased excretion
  - Increased usage without replenishment

Maret W. Zinc in Cellular Regulation: The Nature and Significance of "Zinc Signals". Int J Mol Sci. 2017; 18(11):. [PDF]

Zinc and Depression

- A link has been established in the literature **since the 1980's**
- Zinc is critical in **many areas of the brain**
  - Amygdala, frontal cortex, hippocampus
- Thought to have **anti-inflammatory/antioxidant** properties
  - Shown to ↓ CRP
  - Protect against lipid peroxidation
  - Possibly inhibit NMDA receptors

Wang J, Um P, Dickerman B, Liu J. Zinc, Magnesium, Selenium and Depression: A Review of the Evidence, Potential Mechanisms and Implications Nutrients. 2018; 10(5):584-.

How is Zinc Tested?

- **Plasma Zinc (most common)**
  - Ideal range 90-135ug/dL

- **Low Alkaline phosphatase (functional bonus)**
  - Alk Phos mostly made by liver and bone
  - Zn dependent enzyme

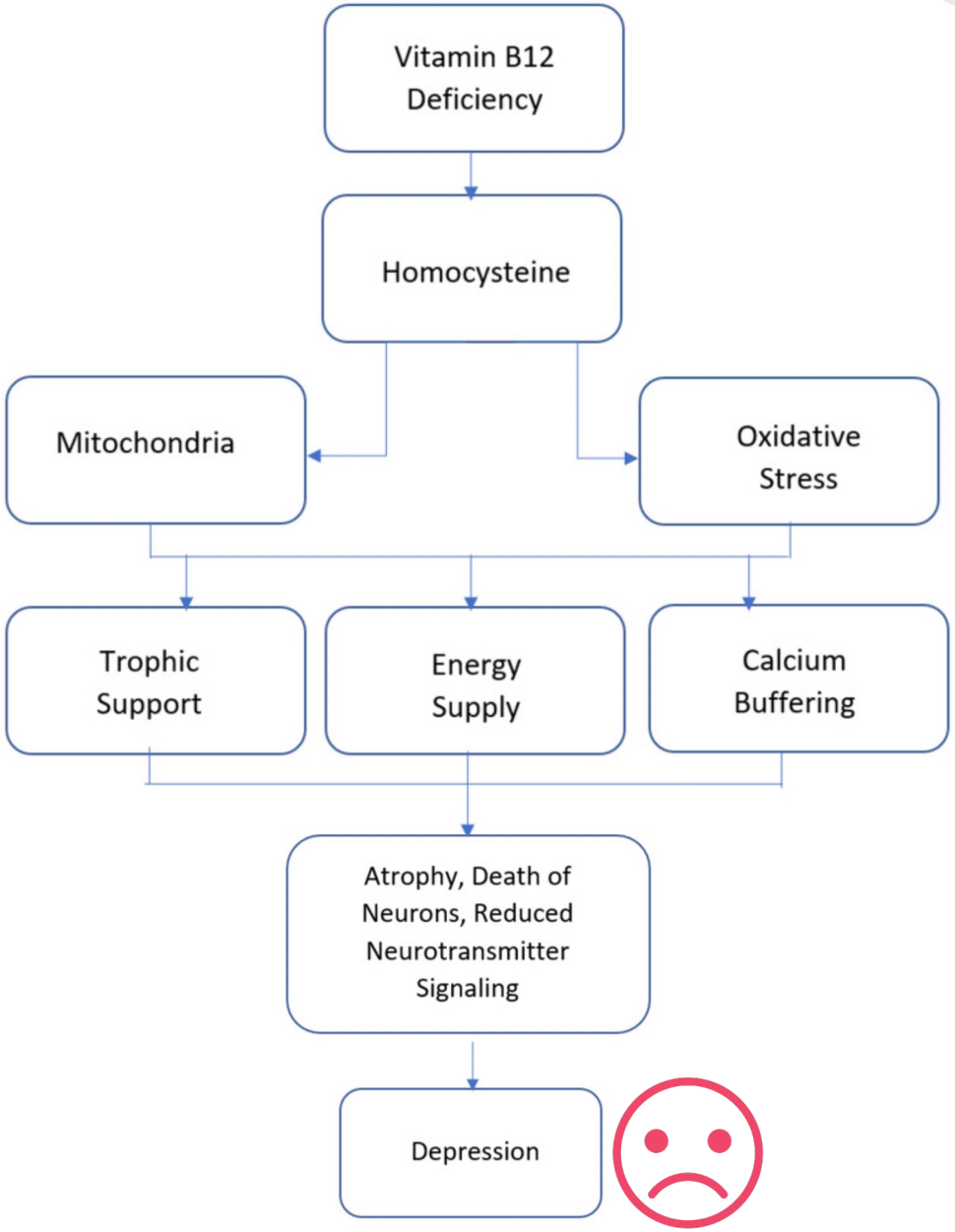
Cho YE, Lomeda RA, Ryu SH, et al. Zinc deficiency negatively affects alkaline phosphatase and the concentration of Ca, Mg and P in rats. Nutr Res Pract. 2007; 1(2):113-9. [PDF]

Zinc dosing:

- **General suggestions:** 15-30mg elemental Zn(or more depending)
  - Common forms: gluconate, citrate, picolinate
  - Divided dosing if doing higher doses
  - Watch nausea (take with food)
- **Be mindful of Copper**
  - Serum Cu/Zn ratio = about 1:1 ug/dL
  - 8-15mg of Zinc per 1mg of Copper (supplement)

Vitamin B12 (Cobalamin)

- Water soluble vitamin
- Common symptoms of deficiency:
  - **Depression**, fatigue, weakness, memory loss, balance issues, peripheral tingling
- **Deficiency due to:**
  - Not eating it
  - Not absorbing it
  - Medications (oral contraceptives, Metformin(Glucophage), H2 blockers)



Sangle P, Sandhu O, Aftab Z, Anthony AT, Khan S. Vitamin B12 Supplementation: Preventing Onset and Improving Prognosis of Depression. Cureus. 2020; 12(10):e11169. [PDF]

How is B12 Tested?

- **Serum B12**
  - Range: 200-900pg/dL

- **Methylmalonic Acid (MMA)**
  - High levels = needs B12
  - Blood range: 0.07-0.27mmol/L
  - Urine range: 0.4 – 2.5 µmol/mmol

B vitamins play well together

Especially B6 and Folate with B12.

Review Article

Vitamin D and Depression: A Critical Appraisal of the Evidence and Future Directions

Vikas Menon, Sujita Kumar Kar[1], Navratan Suthar[2], Naresh Nebhinani[2]

ABSTRACT

Background: Growing evidence points to the role of vitamin D in the pathobiology and treatment of depression. However, the evidence is inconsistent in many aspects. The objectives of this narrative review were to evaluate the state of the evidence, synthesize the knowledge gaps, and formulate recommendations for more enhanced research in this growing area. **Methods:** Electronic searches of MEDLINE via PubMed, Cochrane Library, and Google Scholar databases were carried out from inception till February 2019 to identify relevant English language peer-reviewed articles. Abstracts generated were systematically screened for eligibility. Included articles were grouped under three broad themes: The association between vitamin D and depression, its biological underpinnings, and trials evaluating the efficacy of vitamin D supplementation in depression. Relevant data were extracted as per a structured proforma. **Results:** A total of 61 articles were included in the present review. Overall findings were that there is a relationship between vitamin D and depression, though the directionality of this association remains unclear. The association appears to be driven by the homeostatic, trophic, and immunomodulatory effects of vitamin D. Evidence from supplementation trials suggest a more robust therapeutic effect on subjects with major depression and concurrent vitamin D deficiency. **Conclusion:** Serum vitamin D levels inversely correlate with clinical depression, but the evidence is not strong enough to recommend universal supplementation in depression. Enriching depression treatment trials with subjects having concurrent vitamin D deficiency appears to be a potential step forward in identifying subgroups who may maximally benefit from this approach.

Key words: *Depression, immune system, inflammation, psychiatry, vitamin D*

Indian J Psychol Med. 2020 Jan-Feb; 42(1): 11–21.
Published online 2020 Jan 6. doi: 10.4103/IJPSYM.IJPSYM_160_19

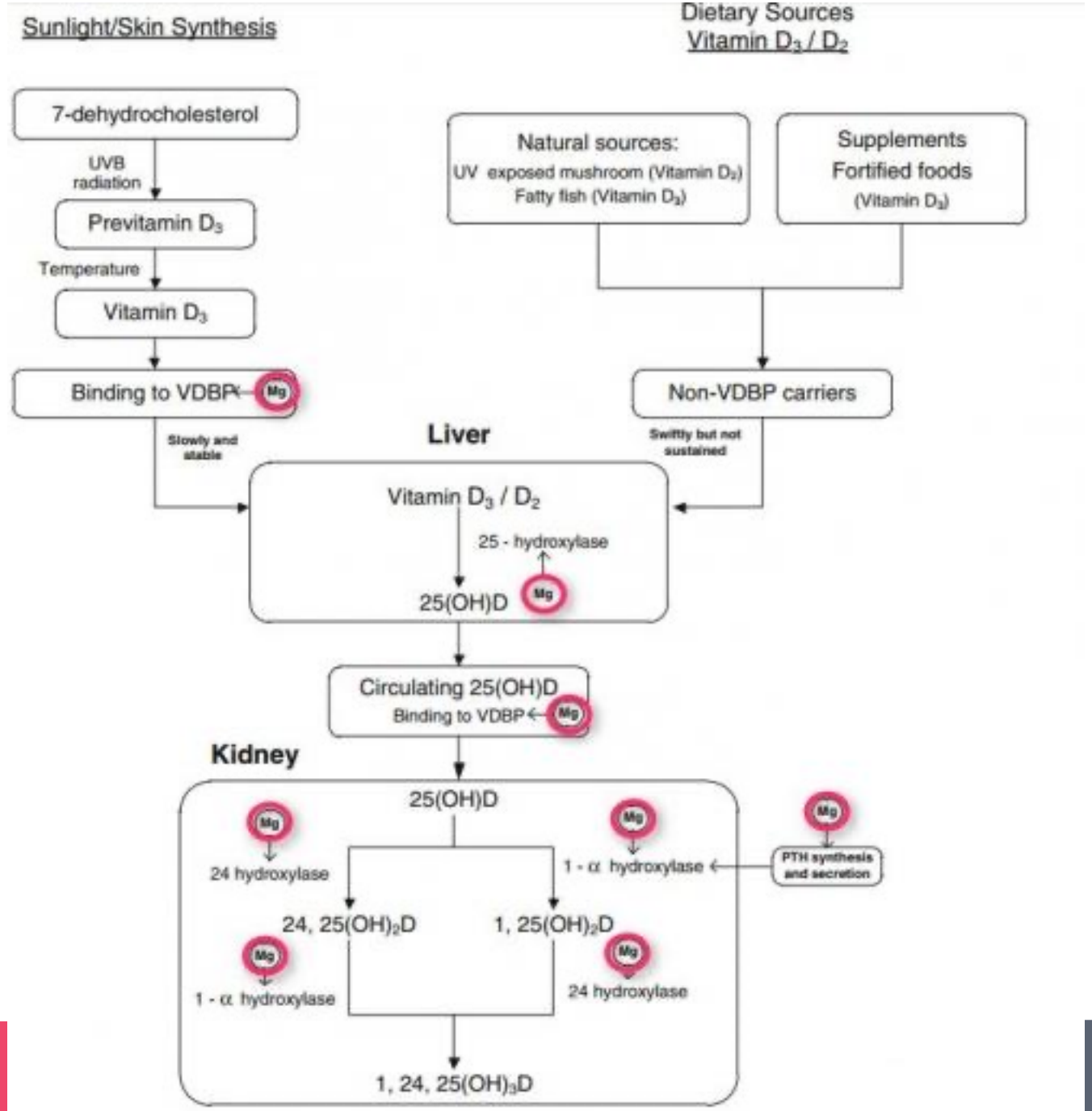
PMCID: PMC6970300
PMID: 31997861

Vitamin D and Depression: A Critical Appraisal of the Evidence and Future Directions

Vikas Menon, Sujita Kumar Kar,[1] Navratan Suthar,[2] and Naresh Nebhinani[2]

“Evidence is not strong enough to recommend universal supplementation in depression…”

- **Then let’s test!**
- Range: 25-80 ng/mL



Reddy P, Edwards LR. Magnesium Supplementation in Vitamin D Deficiency. Am J Ther. 2019; 26(1):e124-e132. [pubmed]

Hormones

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J Thyroid Res. 2012; 2012: 590648.
Published online 2011 Dec 14. doi: 10.1155/2012/590648
PMCID: PMC3246784
PMID: 22220285

The Link between Thyroid Function and Depression

Mirella P. Hage and Sami T. Azar *

Author information Article notes Copyright and License information Disclaimer

Abstract

Go to:

The relation between thyroid function and depression has long been recognized. Patients with thyroid disorders are more prone to develop depressive symptoms and conversely depression may be accompanied by various subtle thyroid abnormalities. Traditionally, the most commonly documented abnormalities are elevated T4 levels, low T3, elevated rT3, a blunted TSH response to TRH, positive antithyroid antibodies, and elevated CSF TRH concentrations. In addition, thyroid hormone supplements appear to accelerate and enhance the clinical response to antidepressant drugs. However, the mechanisms underlying the interaction between thyroid function and depression remain to be further clarified. Recently, advances in biochemical, genetic, and neuroimaging fields have provided new insights into the thyroid-depression relationship.

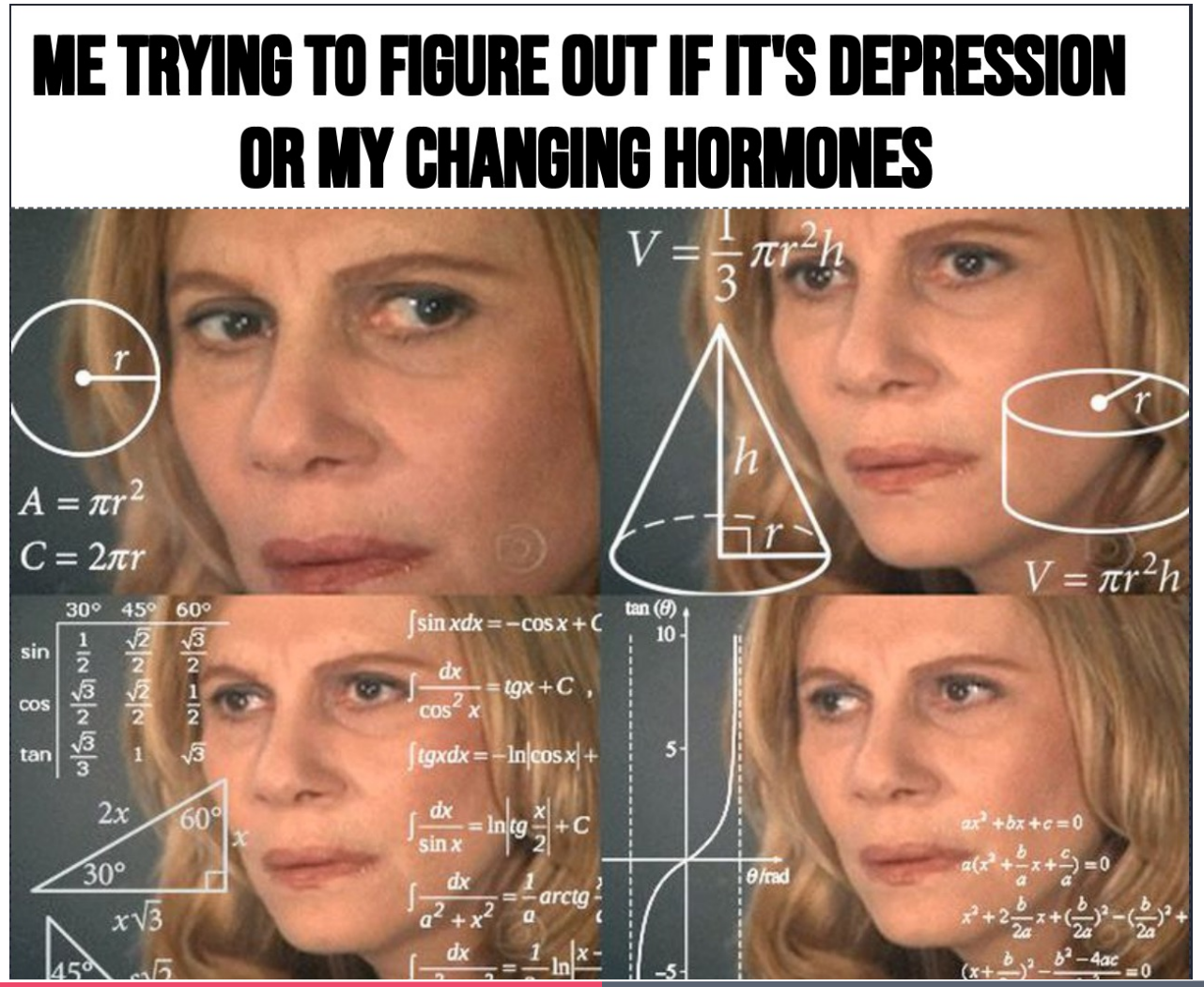
If research proves this, why is TSH alone considered the “gold standard?”

Common Reference Range for Thyroid Markers

Thyroid Marker	Conventional Reference Range	"Optimal Range"
TSH	0.5-4.5mU/L	1.0-2.0(2.5?)mU/L
T4	4.5-12ug/dL	6.0-12ug/dL
Free T4	0.82-1.77ng/dL	1.0-1.77ng/dL
T3	71-180ng/dL	100-180ng/dL
Free T3	2.0-4.4pg/mL	3.0-4.0pgmL
rT3	7.0-24ng/dL	9.2-18ng/dL
fT3/rT3 ratio	--	<0.2 (not on T3)
T3/rT3 ratio	--	<10 (not on T3)
Total T3 Uptake	24-39%	28-38%
Free Thyroxine Index (FTI)	1.2-4.9	1.2-4.9
Anti Thyroglobulin Ab Thyroid Peroxidase Ab	<20 IU/mL <34 IU/mL	<20 <34
Thyroid Stimulating Immunoglobulin Ab	<0.55 IU/L	<0.55 IU/L

Per Labcorp, Quest, Mayoclinic lab ranges

What about Estrogen?



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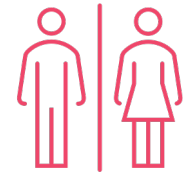
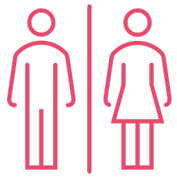
Physiological Estradiol and the Brain:

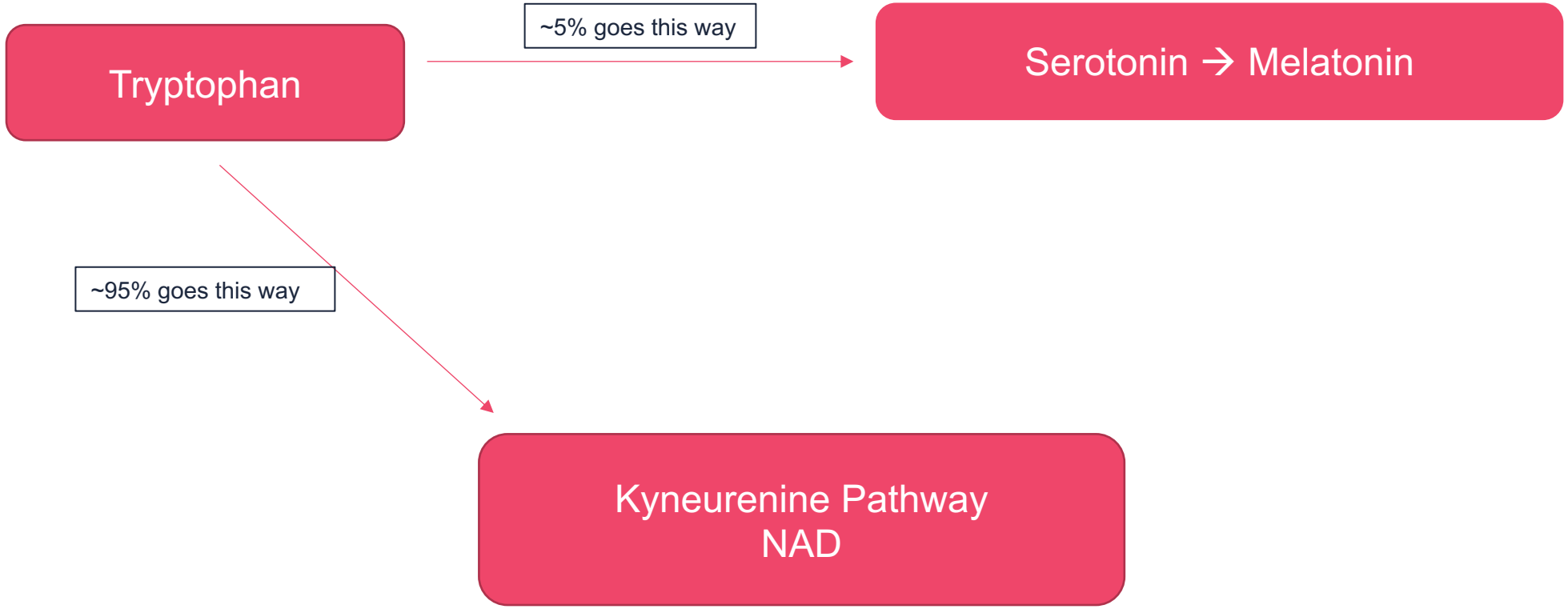


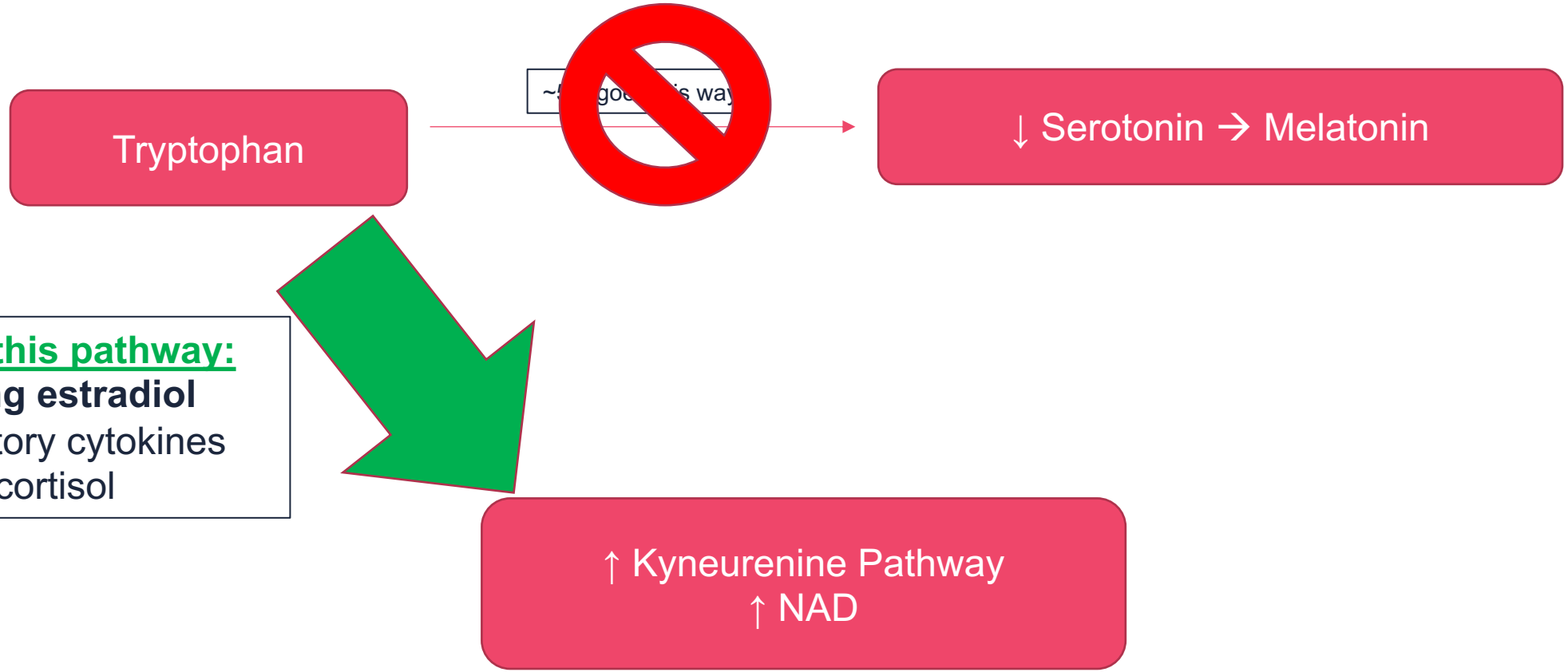
- ↑ mRNA for tryptophan hydroxylase 2 to ↑ tryptophan → 5-HTP
- ↑ serotonin transporters
- Plays a role in MAO-A activity (catecholamine break down)
  - Dopamine, norepinephrine, epinephrine

Hernández-Hernández OT, Martínez-Mota L, Herrera-Pérez JJ, Jiménez-Rubio G. Role of Estradiol in the Expression of Genes Involved in Serotonin Neurotransmission: Implications for Female Depression. Curr Neuropharmacol. 2019; 17(5):459-471. [PDF]

↓ Estradiol = ↓ Serotonin and issues with dopamine, norepinephrine and epinephrine

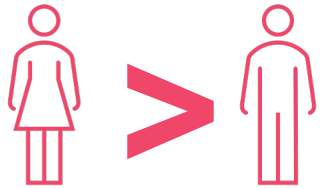



Tryptophan
~5% goes this way
Serotonin → Melatonin
~95% goes this way
Kyneurenine Pathway
NAD


Tryptophan
↓ Serotonin → Melatonin
Stimulates this pathway:
• Increasing estradiol
• Inflammatory cytokines
• Elevated cortisol
↑ Kyneurenine Pathway
↑ NAD

This means

↑ Inflammation, cortisol &/or Estradiol = ↓ Serotonin ☹



Progesterone

b-Pregnanediol

a-Pregnanediol

Ideally with a-pregnanediol

1. Progesterone → alpha and beta pregnanediol

2. a-Pregnanediol → Allopregnanolone (ALLO = neurosteroid)

3. ALLO → crosses the BBB and binds to GABA-A receptors = calming

Schüle C, Nothdurfter C, Rupprecht R. The role of allopregnanolone in depression and anxiety Progress in Neurobiology. 2014; 113:79-87.

ALLO also supports…

"…enhancement of neurogenesis, myelination, neuroprotection, and regulatory effects on HPA axis function."

Schüle C, Nothdurfter C, Rupprecht R. The role of allopregnanolone in depression and anxiety Progress in Neurobiology. 2014; 113:79-87.

Progesterone is often misrepresented

Hormone (serum)	pg/mL	ng/mL
Estradiol (early follicular)	20-150*	0.020-0.150
Estradiol (ovulatory surge)	>200*	>0.20
Estradiol (luteal)	40-200*	0.040-0.20
Estradiol (menopause)	<35*	<0.035
Progesterone (luteal)	2,000-20,000	3-20*

* = most commonly reported units on lab work

Most studies say serum results >3ng/mL indicates ovulation occurred

How much estrogen and progesterone are made?

Estradiol:

Mid-luteal = about 250 mcg/day

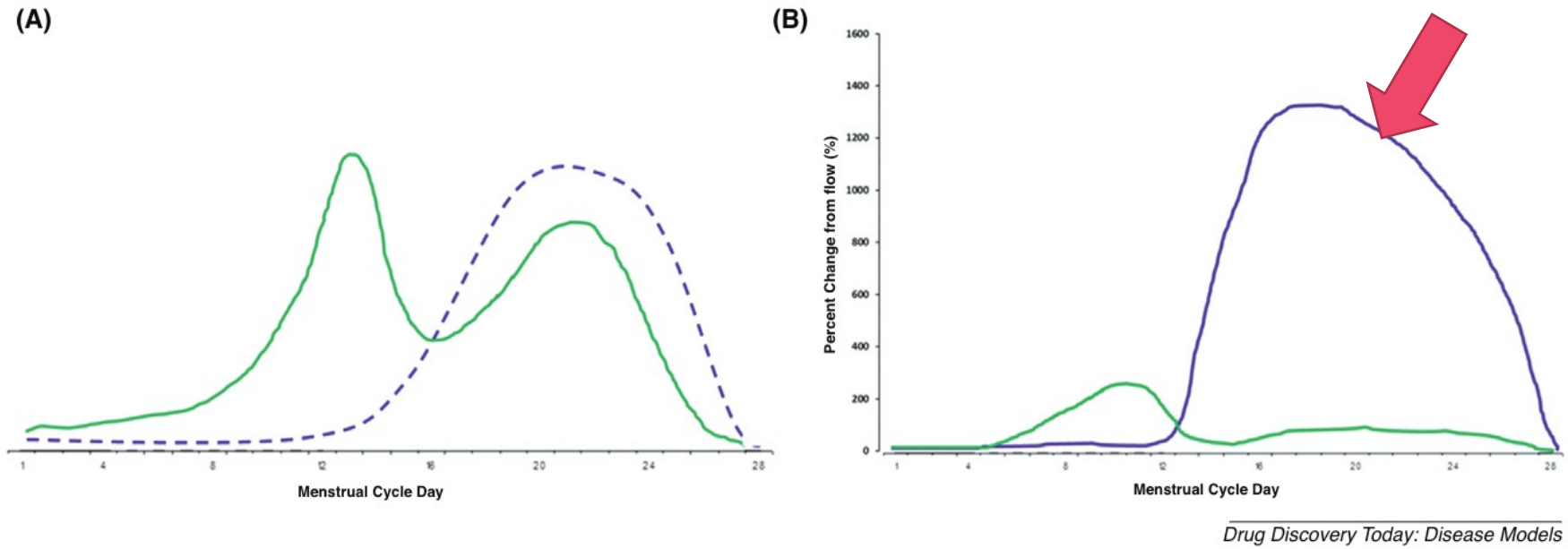
Progesterone:

Mid-luteal = about 25-40mg/day

Progesterone:
Post-Menopause

<1mg/day

Internet Drawing vs Reality of Estradiol to Progesterone



Drug Discovery Today: Disease Models

Prior JC. Women's reproductive system as balanced estradiol and progesterone actions—A revolutionary, paradigm-shifting concept in women's health Drug Discovery Today: Disease Models. 2020; 32:31-40.

Testosterone and Depression

"Testosterone levels may represent one important biomarker for depression risk. In men, lower testosterone has been associated with **higher risk of depression**, and this association has also been shown with the more specific measure of "**free testosterone**" that measures bioactive levels of testosterone not attached to sex hormone-binding globulin (SHBG)."

Määttänen I, Gluschkoff K, Komulainen K, et al. Testosterone and specific symptoms of depression: Evidence from NHANES 2011–2016 Comprehensive Psychoneuroendocrinology. 2021; 6:100044-.

Most of the literature on mood disorders is on males however anecdotally, we know testosterone is important in females too.

“When my testosterone pellet is inserted it’s like a new battery pack. I’m a whole new woman with a whole new mood. Watch out world.”

My former neighbor who is in her late 50’s

Cortisol and Mental Health

- There is a lot of **mixed research** on stress and mental health
- The agreement is that **stress plays a big role**
- The disagreement is how that shows up for cortisol
- **Takeaway:** Test, support them and help them address their stress as best as possible

Nandam LS, Brazel M, Zhou M, Jhaveri DJ. Cortisol and Major Depressive Disorder—Translating Findings From Humans to Animal Models and Back Front. Psychiatry. 2020; 10.

Pubmed search:

- **Stress + Mental**
  - 1914-current → 235,170 searches
- **Stress + Depression**
  - 1922-current → 87,633 searches
- **Stress + Anxiety**
  - 1946-current → 69,384 searches

Stress vs. Anxiety

Stress	Both Stress and Anxiety	Anxiety
• Generally is a response to an *external* cause, such as taking a big test or arguing with a friend. • Goes away once the situation is resolved. • Can be positive or negative. For example, it may inspire you to meet a deadline, or it may cause you to lose sleep.	Both stress and anxiety can affect your mind and body. You may experience symptoms such as: • Excessive worry • Uneasiness • Tension • Headaches or body pain • High blood pressure • Loss of sleep	• Generally is *internal*, meaning it's your reaction to stress. • Usually involves a persistent feeling of apprehension or dread that doesn't go away, and that interferes with how you live your life. • Is constant, even if there is no immediate threat.

https://www.nimh.nih.gov/health/publications/so-stressed-out-fact-sheet

The cortisol awakening response and major depression: Examining the evidence.

Database: APA PsycInfo Journal Article

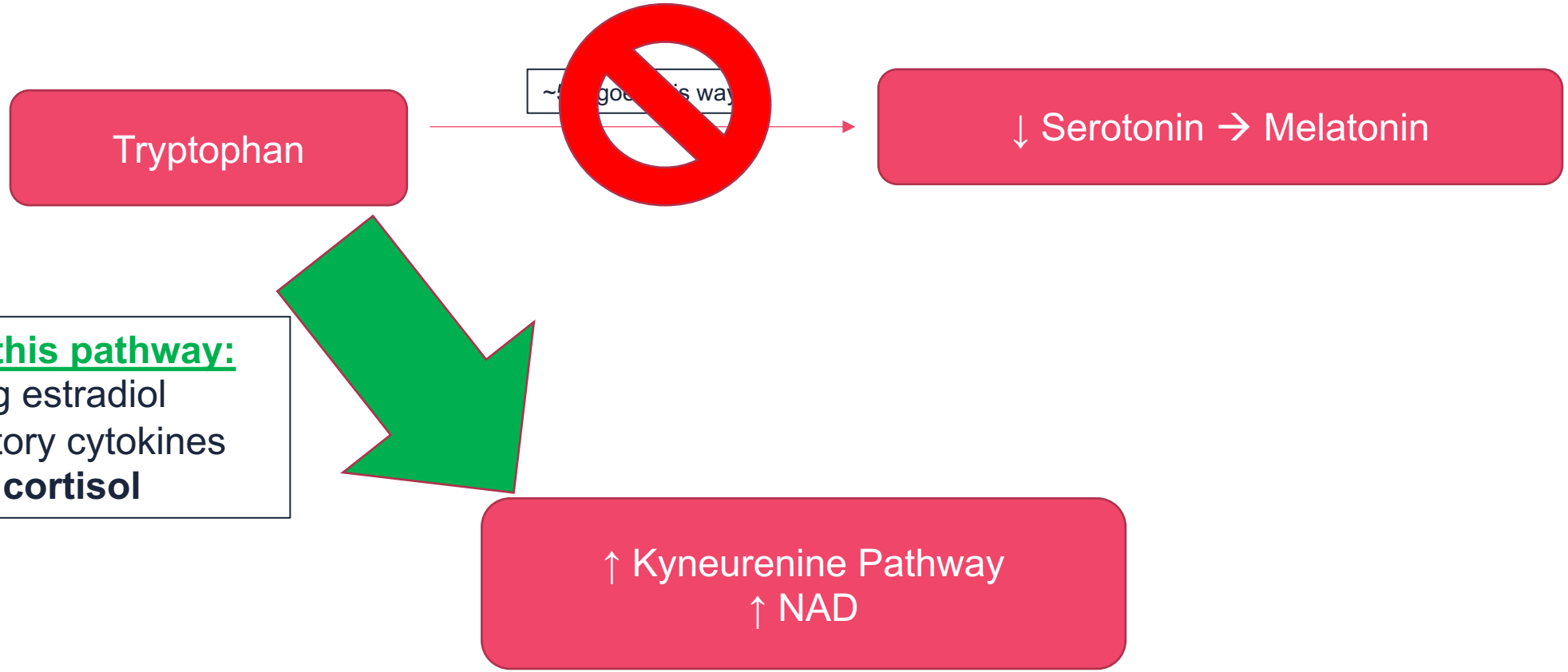
Dedovic, Katarina Ngiam, Janice

Citation

Dedovic, K., & Ngiam, J. (2015). The cortisol awakening response and major depression: Examining the evidence. *Neuropsychiatric Disease and Treatment, 11,* Article 1181-1189.

Abstract

A vast body of literature has revealed that dysregulation of the hypothalamic–pituitary–adrenal (HPA) stress axis is associated with etiology of major depressive disorder (MDD). There are many ways that the dysregulation of the HPA axis can be assessed: by sampling diurnal basal secretion and/or in response to a stress task, pharmacological challenge, and awakening. Here, we focus on the association between cortisol awakening response (CAR), as one index of HPA axis function, and MDD, given that the nature of this association is particularly unclear. Indeed, in the following selective review, we attempt to reconcile sometimes-divergent evidence of the role of CAR in the pathway to depression. We first examine association of CAR with psychological factors that have been linked with increased vulnerability to develop depression. Then, we summarize the findings regarding the CAR profile in those with current depression, and evaluate evidence for the role of CAR following depression resolution and continued vulnerability. Finally, we showcase longitudinal studies showing the role of CAR in predicting depression onset and recurrence. Overall, the studies reveal an important, but complex, association between CAR and vulnerability to depression. (PsycInfo Database Record (c) 2021 APA, all rights reserved)


Tryptophan
↓ Serotonin → Melatonin
↑ Kyneurenine Pathway
↑ NAD
Stimulates this pathway:
• Increasing estradiol
• Inflammatory cytokines
• Elevated cortisol

This means
↑ Inflammation, cortisol &/or estradiol = ↓ Serotonin ☹

Microbiome

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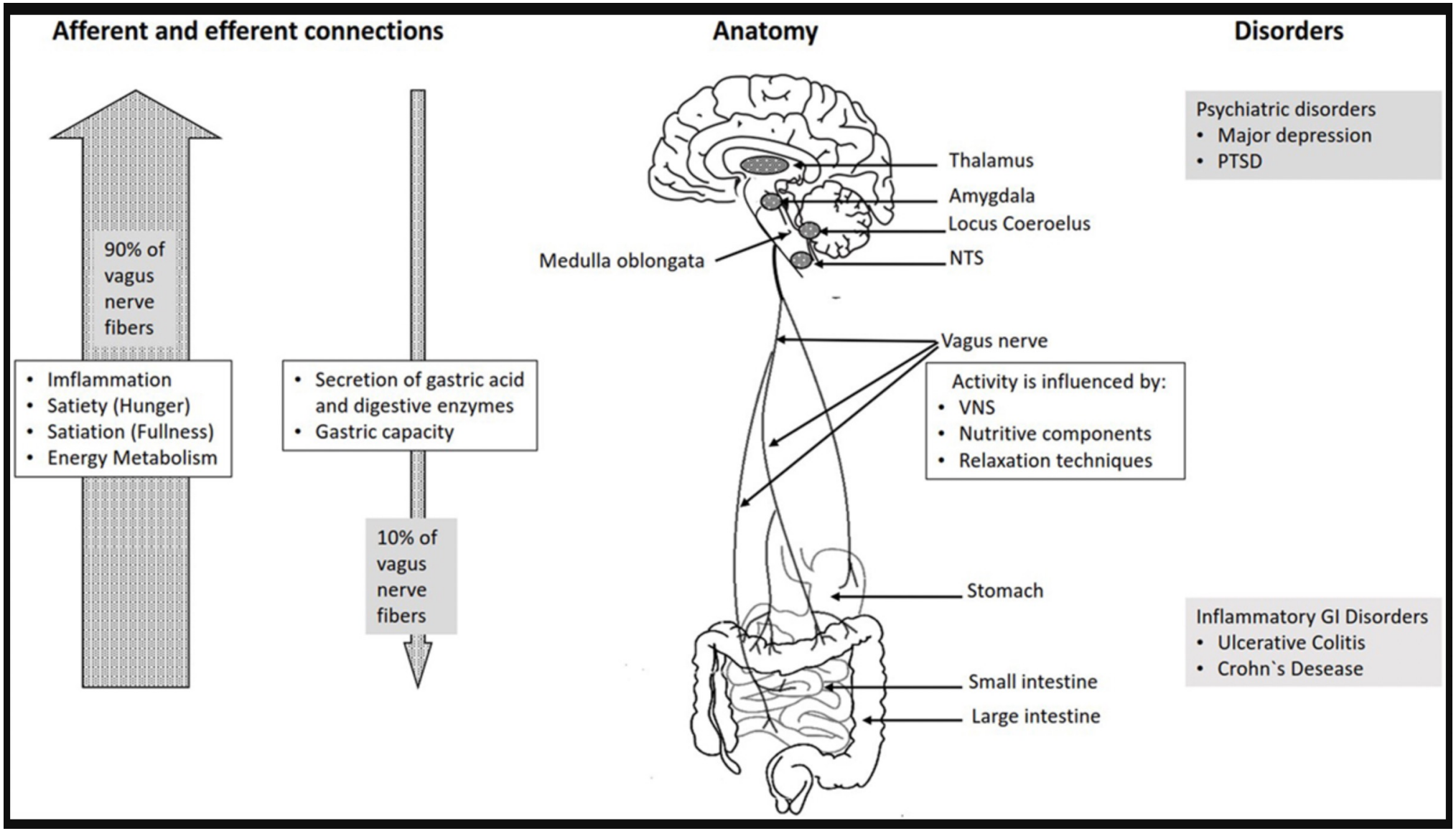


Breit S, Kupferberg A, Rogler G, Hasler G. Vagus Nerve as Modulator of the Brain–Gut Axis in Psychiatric and Inflammatory Disorders Front. Psychiatry. 2018; 9.

“Any permutations in the gut microbiome composition trigger microbial **lipopolysaccharides (LPS)** production. It, in turn, activates inflammatory responses. Cytokines send signals to the vagus nerve, which links the process to the hypothalamic-pituitary-adrenal axis that consequently causes **behavioral effects.** Another school of thought suggests that the gastrointestinal (GI) tract's inflammation leads to **neuroinflammation**. It then fuels microglial action and triggers the kynurenine pathway. All these processes **induce depression.** In human studies, evidence of changes in microflora composition explains depression. The bidirectional connection between gut microflora and depression has been well reinforced by research.”

Limbana T, Khan F, Eskander N. Gut Microbiome and Depression: How Microbes Affect the Way We Think. Cureus. 2020; 12(8):e9966. [PDF]

Lipopolysaccharides (LPS)

- Essential component of the outer membrane of **gram-negative bacteria**
  - Lipid A: an **endotoxin** and main virulence factor
  - Major microbial trigger of the **innate immune system**
  - Does not seem to damage the gut epithelium itself, but once it crosses through into the bloodstream it's a problem

- **Common:** Pseudomonas, Klebsiella, Proteus, Salmonella, Providencia, Escherichia, H. Pylori, Morganella, Aeromonas, and Citrobacter

Zielen S, Trischler J, Schubert R. Lipopolysaccharide challenge: immunological effects and safety in humans Expert Review of Clinical Immunology. 2015; 11(3):409-418.

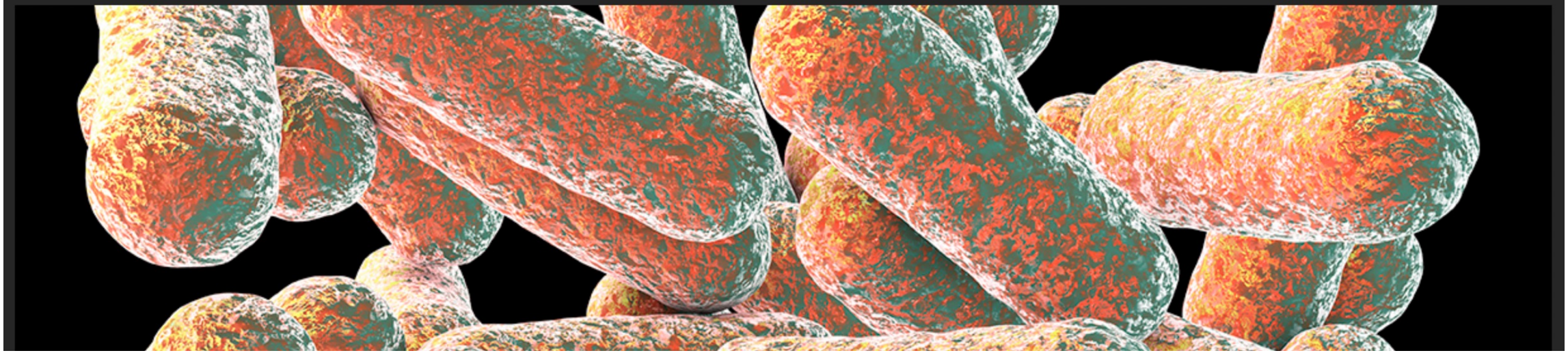
Morganella and Klebsiella

NEWS | BIOLOGY

Gut microbe linked to depression in large health study

Result brings researchers a step closer to harnessing microbes to combat mood disorders

4 FEB. 2022 · :45 PM · BY ELIZABETH PENNISI



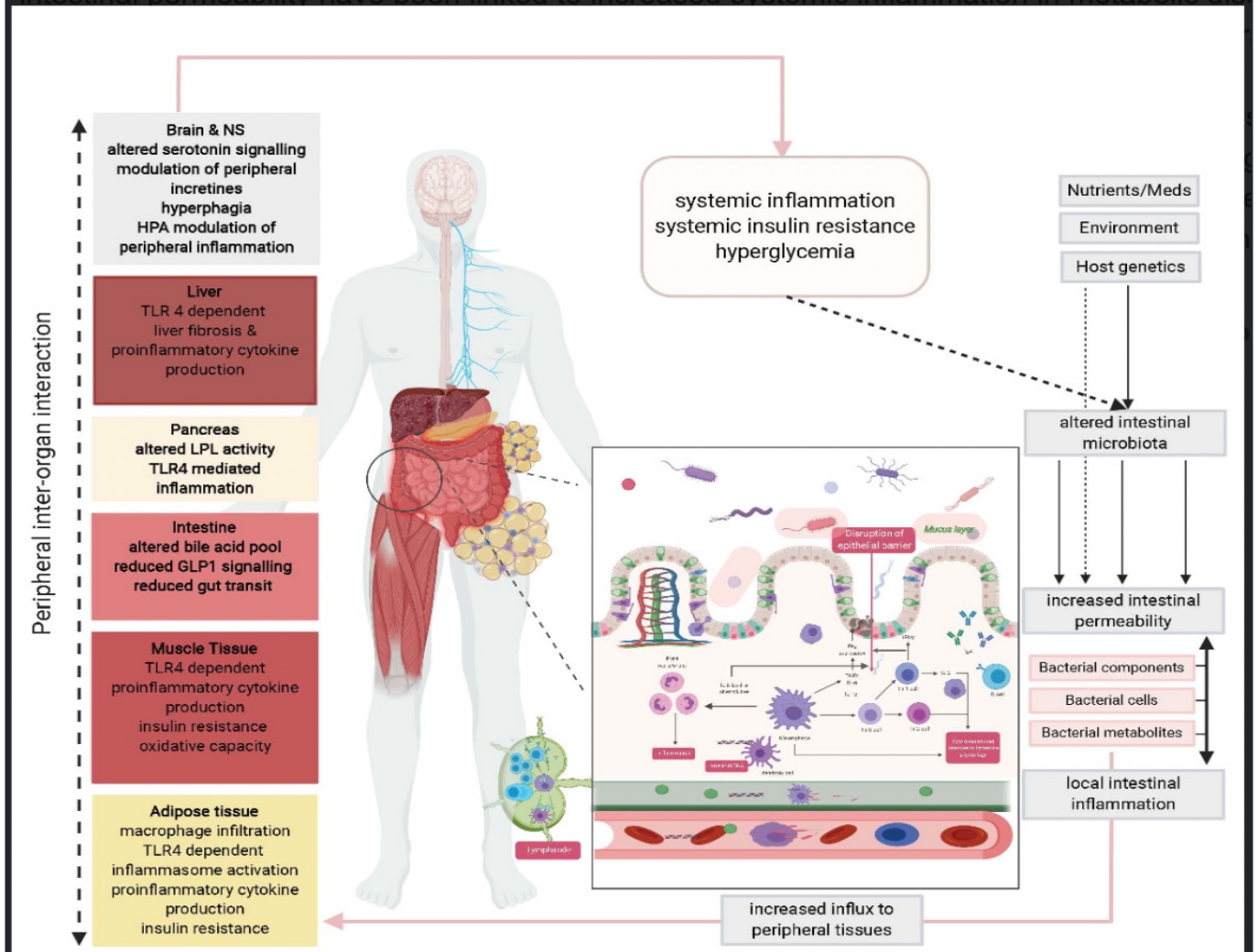
https://www.science.org/content/article/gut-microbe-linked-depression-large-health-study

“LPS is a potent endotoxin that binds to cell surface receptors such as TLR4/CD14/MD2 that induces the secretion of proinflammatory cytokines, nitric oxide, and eicosanoids. The presence of LPS in the blood or interstitial fluid can lead to endotoxemia through Lipid A moiety, which can cause **septic shock** under exaggerated immune response.

Recently, a low dose of LPS exposure has correlated with **autoimmune diseases, and allergies** while high concentrations of LPS in the blood lead to **metabolic syndrome**. This increases the risk of serious diseases such as **type 2 diabetes, heart diseases, and liver diseases**…Specific opportunistic pathogens like *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex bacteria, *Helicobacter pylori*, and *Salmonella enterica* can adapt through LPS structure-function changes to develop a chronic infection in the **respiratory and gastrointestinal** tract.

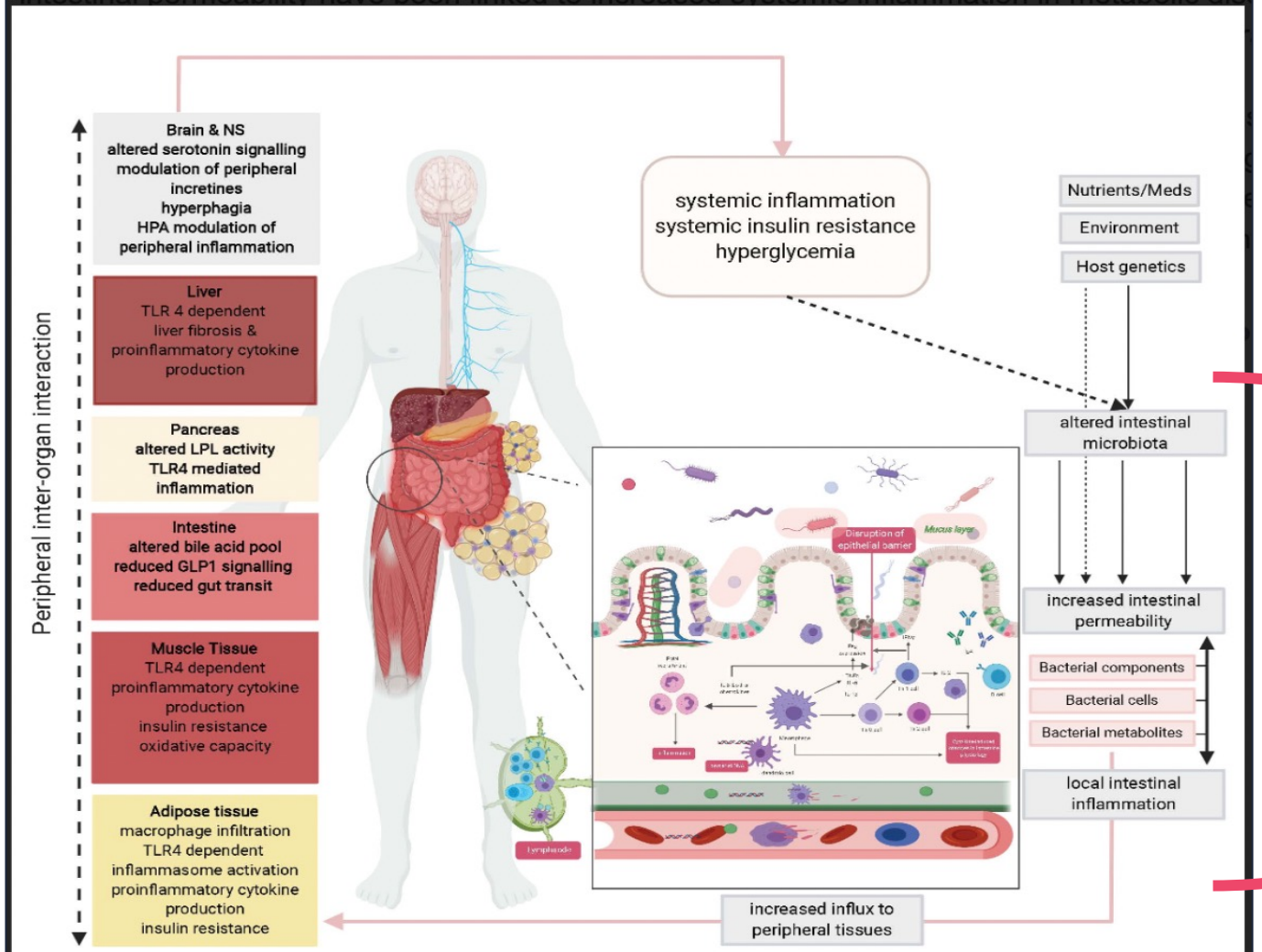
Recently, research has demonstrated that LPS induces membrane lipid disturbances, which affect cholesterol interacting proteins, lipoprotein metabolism, and membrane apo E/amyloid-beta interactions. These alterations predispose to **hypercholesterolemia, dyslipidemia, and non-alcoholic fatty liver disease.** In some cases, the presence of LPS can interfere with the clearance of toxins from the body linking it to **neurological degeneration**.”

Farhana A, Khan YS. Biochemistry, Lipopolysaccharide . State Pearls. 2022; [pubmed]



- Gut microbiota shifts in metabolic disease, diet and increased intestinal permeability are highly interlinked
- Intestinal permeability impairment ensues from damage to the immunologic, secretory and epithelial barrier of the gut and is associated with inflammation and metabolic impairment in key metabolic tissues
- Bacterial translocation is poorly defined and there is accumulating evidence for extra-intestinal bacterial presence, which may contribute to organ dysfunction in metabolic disease and entertaining systemic inflammation

Chakaroun R, Massier L, Kovacs P. Gut Microbiome, Intestinal Permeability, and Tissue Bacteria in Metabolic Disease: Perpetrators or Bystanders? Nutrients. 2020; 12(4):1082-.



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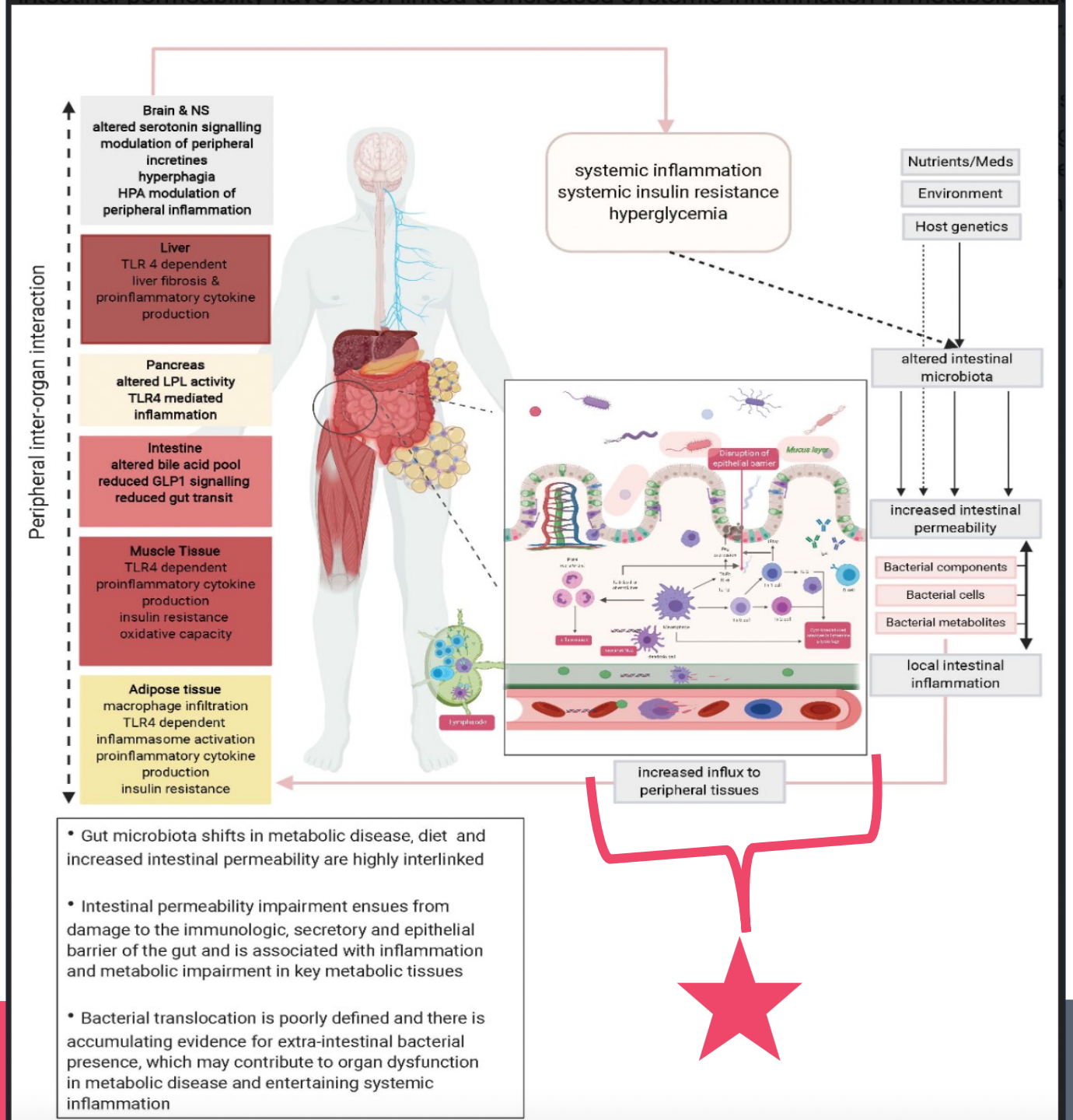

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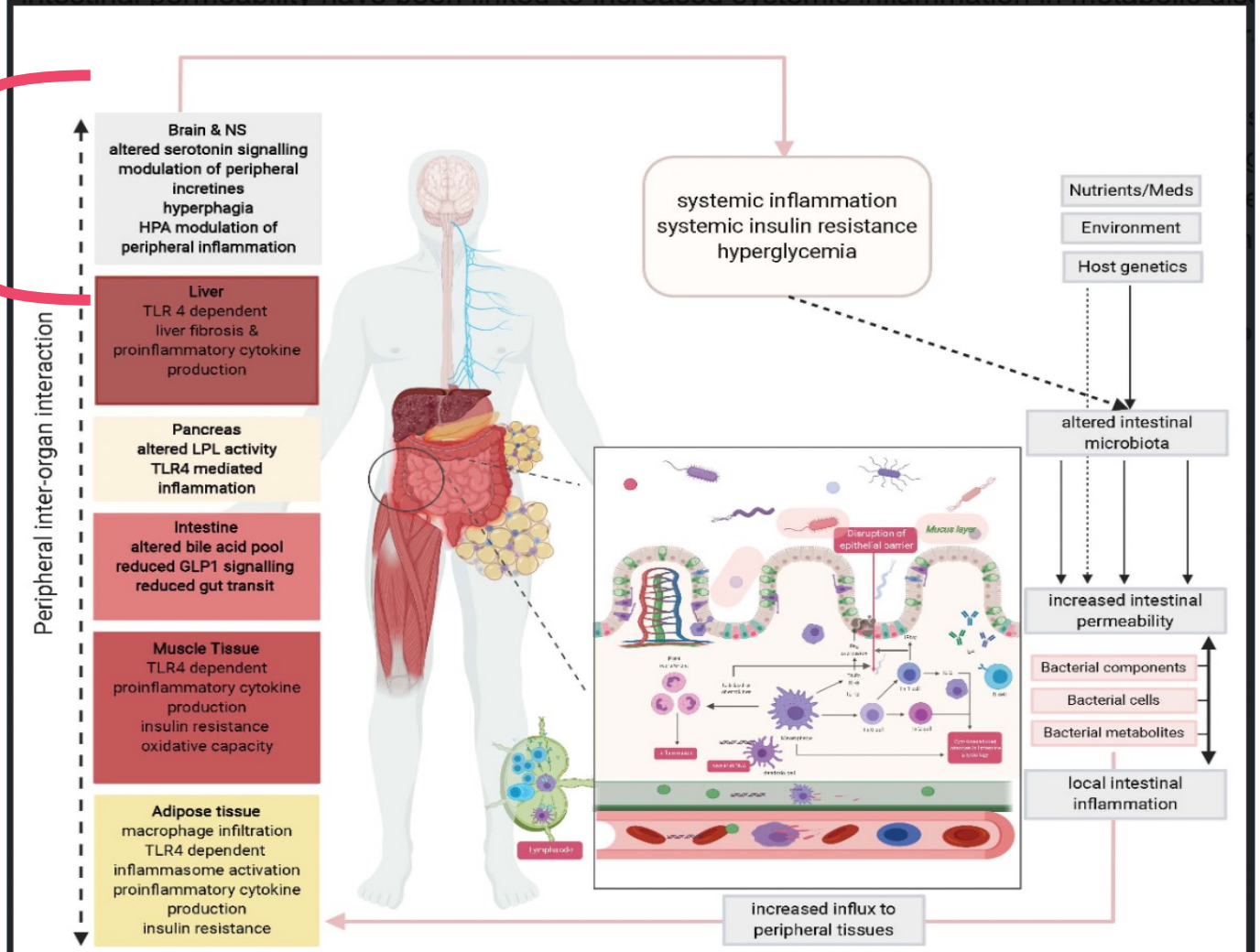

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Chakaroun R, Massier L, Kovacs P. Gut Microbiome, Intestinal Permeability, and Tissue Bacteria in Metabolic Disease: Perpetrators or Bystanders? Nutrients. 2020; 12(4):1082-.

Zonulin

- Discovered in 2000 by Dr. Alessio Fasano & his team
- A **major intestinal permeability modulator**
  - Paracellular tight junctions regulate antigen crossing through the intestinal barrier
  - High levels of zonulin can disrupt this
- **2 major causes of increased zonulin**:
  - Bacterial overgrowth (LPS)
  - Gluten

Fasano A. All disease begins in the (leaky) gut: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases. F1000Res. 2020; 9:. [PDF]

Secretory IgA(SIgA)

- Mostly made by plasma cells in lamina propria (GALT) of intestinal villi
- **Role:**
  - Increases with food and microbial (bacterial, viral, parasitic) antigens
  - First line of defense against pathogens
  - Facilitates mucus surface colonization by commensal microbiota
  - Regulates intestinal microbiota maturation
  - Helps regulate immune homeostasis

- "In steady-state conditions, approximately 36% of the gut microbiota is coated with SIgA, whereas during inflammation, this number can increase up to 69%" Pietrzak B, Tomela K, Olejnik-Schmidt A, Mackiewicz A, Schmidt M. Secretory IgA in Intestinal Mucosal Secretions as an Adaptive Barrier against Microbial Cells. Int J Mol Sci. 2020; 21(23):. [PDF]

Gastroenterol Hepatol (N Y). 2017 Mar; 13(3): 164–169.

PMCID: PMC5439135

PMID: 28539843

Considering the Bidirectional Pathways Between Depression and IBD: Recommendations for Comprehensive IBD Care

Laurie Keefer, PhD and Sunanda V. Kane, MD, MSPH

Author information Copyright and License information Disclaimer

Abstract

Go to:

Because of disease chronicity and required shifts in coping and self-management skills over time, it is not surprising that patients with inflammatory bowel disease (IBD) are at increased risk for mental health issues, including depression. Modern conceptualizations of chronic care recognize that the relationship between depression and disease is bidirectional, with (1) poor health leading to poor self-management just as often as poor self-management leads to poor health and (2) inflammation driving depression and depression driving inflammation. Depression in the setting of IBD has been undertreated in this population in the past and, if it remains as such, will continue to pose a significant risk to the current health care system. In this article, we explore these bidirectional relationships and make recommendations for the assessment and treatment of depression in the context of IBD.

Calprotectin

- Majorly studied marker for GI inflammation, **specifically IBD**
  - Considered **neutrophil** specific – as inflammation ↑, the number of neutrophils ↑ resulting in release of cytosolic granules (like calprotectin)

Bjarnason I. The Use of Fecal Calprotectin in Inflammatory Bowel Disease. Gastroenterol Hepatol (N Y). 2017 Jan; 13(1): 53–56.

Are there other GI markers that might be an issue?

- Of course!
- Parasites
- Worms
- Candida

In summary:

- Depression, anxiety, etc. are **multi-faceted.**
- **Neuroinflammation** is a big trigger.
- **Gut inflammation** goes to the brain and creating neuroinflammation.
- **Hormones** play a big role in the function of our brain and our mood.
- If research has known these triggers for decades, then please properly **work them up.**

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Thank you for listening!

Carrie Jones, ND, FABNE, MPH